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Discovering common pathogenetic processes between COVID-19 and tuberculosis by bioinformatics and system biology approach

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Introduction: The coronavirus disease 2019 (COVID-19) pandemic, stemming from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has persistently threatened the global health system. Meanwhile, tuberculosis (TB) caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) still continues to be endemic in various regions of the world. There is a certain degree of similarity between the clinical features of COVID-19 and TB, but the underlying common pathogenetic processes between COVID-19 and TB are not well understood.

Methods: To elucidate the common pathogenetic processes between COVID-19 and TB, we implemented bioinformatics and systematic research to obtain shared pathways and molecular biomarkers. Here, the RNA-seq datasets (GSE196822 and GSE126614) are used to extract shared differentially expressed genes (DEGs) of COVID-19 and TB. The common DEGs were used to identify common pathways, hub genes, transcriptional regulatory networks, and potential drugs.

Results: A total of 96 common DEGs were selected for subsequent analyses. Functional enrichment analyses showed that viral genome replication and immune-related pathways collectively contributed to the development and progression of TB and COVID-19. Based on the protein-protein interaction (PPI) network analysis, we identified 10 hub genes, including IFI44L, ISG15, MX1, IFI44, OASL, RSAD2, GBP1, OAS1, IFI6, and HERC5. Subsequently, the transcription factor (TF)-gene interaction and microRNA (miRNA)-gene coregulatory network identified 61 TFs and 29 miRNAs. Notably, we identified 10 potential drugs to treat TB and COVID-19, namely suloctidil, prenylamine, acetohexamide, terfenadine, prochlorperazine, 3'-azido-3'-deoxythymidine, chlorophyllin, etoposide, clioquinol, and propofol.

Conclusion: This research provides novel strategies and valuable references for the treatment of tuberculosis and COVID-19.

KEYWORDS

SARS-CoV-2, tuberculosis, differentially expressed genes, protein-protein interaction (PPI), hub gene, drug molecule

Introduction

Coronavirus disease 2019 (COVID-19), resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an atypical respiratory disease (Pollard et al., 2020). According to the World Health Organization (WHO), as of January 2023, there have been more than 659 million confirmed cases and over 6.6 million deaths worldwide. The common symptoms of COVID-19 include fever, dyspnea, dizziness, upper airway congestion, dry cough, and sputum production (Jin et al., 2020). Additionally, vomiting, headaches, dizziness, loss of taste and smell, and diarrhea have also been reported (Shi et al., 2020; Spinato et al., 2020). The primary mode of SARS-CoV-2 transmission is through respiratory droplets released when an infected person sneezes or coughs, potentially infecting individuals in close proximity (Umakanthan et al., 2020). SARS-CoV-2 belongs to the β coronaviruses and is composed of four structural proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E) (Chan et al., 2020). The spike protein plays a critical role in binding to host cell receptors and facilitating the fusion of cellular and viral membranes. Angiotensin-converting enzyme 2 (ACE2) is a pivotal receptor for SARS-CoV-2's invasion of host cells and is abundantly present in the bladder, heart, lung, kidney, and ileum (Chen et al., 2020; Gheblawi et al., 2020; Zou et al., 2020). Certain preexisting conditions substantially elevate the risk of severe complications and mortality among COVID-19 patients (Huang et al., 2023b; Huang et al., 2023a; Song et al., 2023).

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), is a grave infectious disease that poses a significant threat to global public health due to its high global mortality and morbidity rates (Behr et al., 2021). TB can affect individuals of all age groups and both sexes, with adult men constituting 56% of all TB cases (Chakaya et al., 2021). TB is a severe infectious pulmonary disorder, resulting in pulmonary consolidation, cavitary lesions, and bronchial wall thickening (Deshpande et al., 2020). Furthermore, COVID-19 patients with active pulmonary tuberculosis face a higher risk of mortality due to compromised lung immunity in comparison to patients without tuberculosis (Aggarwal et al., 2021). Additionally, individuals with severe COVID-19 are at greater risk of TB infection compared to those with milder cases (Gao et al., 2021). These studies illustrate that there is a strong interaction and association between TB and COVID-19.

As our understanding of these diseases has deepened, numerous similarities between TB and COVID-19 have been discovered in terms

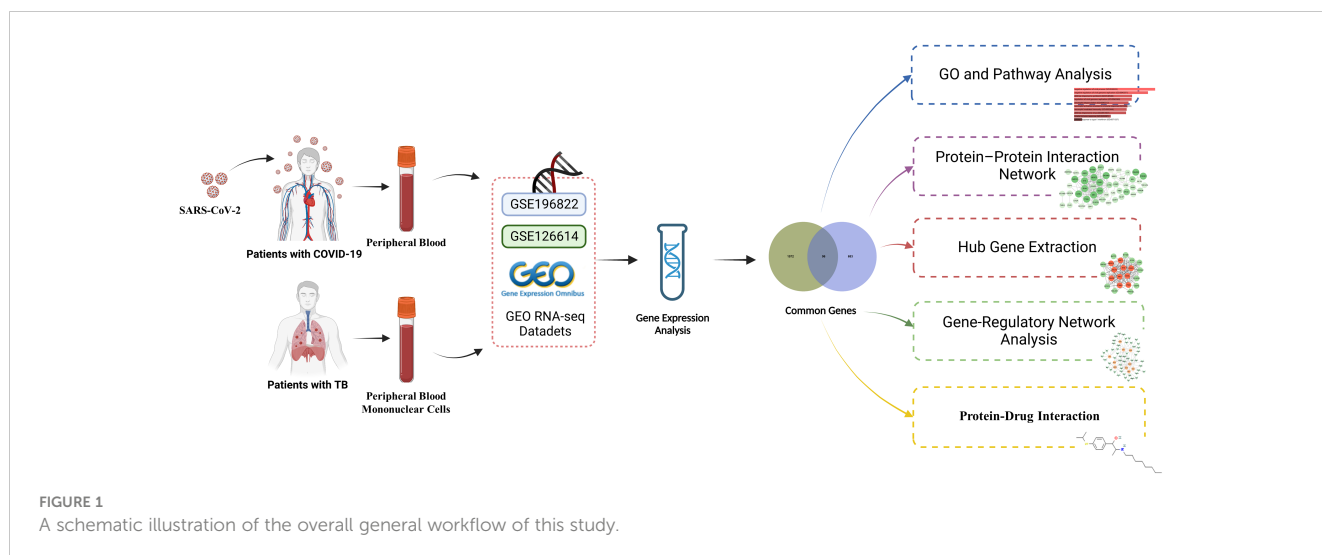
of pathogenesis, clinical symptoms, and sequelae. Within host cells, both *M. tuberculosis* and SARS-CoV-2 can induce proinflammatory cytokines, potentially leading to a cytokine storm if not properly regulated, and they share similar mechanisms for evading the immune system and host cell responses (Zhai et al., 2019; Ragab et al., 2020; Callaway, 2021). Notably, *M. tuberculosis* infection boosts the expression of ACE2, causing significantly severe multi-organ injury (Ziegler et al., 2020). Bacillus Calmette–Guérin (BCG), a weakened live vaccine against *M. tuberculosis*, is helpful in decreasing the proportion of incidence of SARS-CoV-2 IgG seroconversion and clinical symptoms in COVID-19 patients (Benn et al., 2013; Rivas et al., 2021).

Exploring the transcriptional profiles of TB and COVID-19 may provide new insights into the common pathogenesis of the two diseases. The TB datasets (GSE126614) and COVID-19 datasets (GSE196822) were obtained from the Gene Expression Omnibus (GEO) database. Then differentially expressed genes (DEGs) in TB and COVID-19 were filtered, and their shared DEGs were identified to investigate their functions in these two diseases. In addition, we utilized the common DEGs to establish a protein–protein interaction (PPI) network chart and extracted the hub genes, which are used for the recognition of engaged transcription factors (TF), microRNAs (miRNA), and the prediction of potential drugs. The sequential workflow of the analysis is presented in Figure 1.

Methods

Data sources

To determine common pathogenetic processes among TB and COVID-19, we used RNA-seq datasets from the GEO database of the National Center for Biotechnology Information (NCBI, <https://www.ncbi.nlm.nih.gov/geo/>) (Barrett et al., 2013). The GEO accession number of the COVID-19 dataset was GSE196822, which was transcriptional profiling of the peripheral blood of 34 patients with COVID-19 and nine healthy individuals. The COVID-19 dataset was obtained through high-throughput sequencing on the Illumina HiSeq 4000 platform (*Homo sapiens*) for extracting RNA sequences (Huang et al., 2023a; Li et al., 2022). For the TB dataset, we utilized the GEO accession ID of GSE126614 (Del Rosario et al., 2022), which contains the transcriptomic profiles for peripheral blood mononuclear cells from 19 healthy controls and 20 patients with active TB infection. The TB dataset was



obtained through high-throughput sequencing on the Illumina HiSeq 2000 system (*Homo sapiens*). [Supplementary Tables S1, S2](#) show the baseline characteristics of samples in COVID-19 and TB.

Identification of DEGs and common DEGs in COVID-19 and TB

A statistically significant difference between diverse test circumstances at the transcriptional level is generally accepted as the criterion for determining whether the genes are expressed differently ([Kvam et al., 2012](#)). The DEGs were detected from the expression read count values by the DESeq2 R package with a Benjamini–Hochberg correction to control the false discovery rate (FDR) ([Love et al., 2014](#)). The main role of the analysis is to acquire DEGs for the GSE196822 and GSE126614 datasets. The genes that comply with $|\log_2 \text{Fold Change}| > 1$ and $\text{FDR} < 0.05$ were viewed as significantly DEGs. The mutual DEGs of GSE196822 and GSE126614 were obtained by Jvenn (<http://jvenn.toulouse.inra.fr/app/example.html>), an online Venn analysis program ([Bardou et al., 2014](#)).

Gene ontology and pathway enrichment analysis

Gene enrichment analysis is a considerable systematic effort to illuminate and categorize shared biological knowledge ([Subramanian et al., 2005](#)). EnrichR (<https://maayanlab.cloud/enrichr/>) is a versatile web-based tool that was used to identify gene ontology functional enrichment (biological processes (BP), molecular function (MF), and cellular component (CC)) and signaling pathway enrichment to clarify potential biological mechanisms of common DEG ([Kuleshov et al., 2016](#)). Three databases (Bioplanet, Kyoto Encyclopedia of Genes and Genomes (KEGG), and WikiPathways) were used for pathway enrichment analysis.

PPI network analysis and hub gene extraction

STRING (version 11.5), a protein interaction database, was utilized to build the PPI network using common DEGs to describe the physical and functional relationship between COVID-19 and TB ([Szkłarczyk et al., 2019](#)). The medium confidence score set in the analysis was 0.400 to conduct the PPI network. Cytoscape (version 3.9.1) was applied to visualize and process the PPI network ([Smoot et al., 2011](#)).

Hub gene extraction

The PPI network covers edges, nodes, and their links. In this network, the most prominent nodes are supposed to be hub genes. Cytohubba (<http://apps.cytoscape.org/apps/cytohubba>), a remarkable plug-in in Cytoscape, is used for analyzing nodes and the relationships between them in the PPI network ([Ma et al., 2021](#)). Applying the Maximal Clique Centrality (MCC) method of Cytohubba, we confirmed the top 10 genes within the PPI network as the hub genes.

Gene-regulatory network analysis

Transcription factors are proteins that can specifically identify the corresponding genes and control the transcription rate ([Rustad et al., 2014](#)). The gene–TF interaction network was conducted by NetworkAnalyst (<http://www.networkanalyst.ca>) ([Zhou et al., 2019](#)). The topologically credible TFs within the network that were inclined to bind to specific hub genes were from the JASPAR database. JASPAR is an open-access database that contains TF profiles from six taxonomic groups ([Fornes et al., 2020](#)). Moreover, miRNAs targeting gene interaction were used to identify miRNAs that have the potential to regulate the hub genes at the post-transcriptional level. MiRTarBase is one of the most known gene–miRNA interplay repositories ([Huang et al., 2020](#)). From the miRNA–gene interaction via NetworkAnalyst, we

retrieved the miRNAs that can interplay with hub genes concentrated on topological analysis from the miRTarBase database (v 8.0). In Cytoscape, the gene–TF and the gene–miRNA interaction networks were visualized.

Identification of candidate drugs

The identification of drug molecules is one of the most crucial parts of the research. Based on the hub genes of TB and COVID-19, the drug molecule was discovered using the Drug Signatures Database (DSigDB) via EnrichR. DSigDB is a data management repository for recognizing the chemical compounds of the medicine that correspond with the genes (Yoo et al., 2015). The drug function of EnrichR provides easy access to the DSigDB database.

Results

Identification of DEGs and shared DEGs between COVID-19 and TB

To investigate the common pathogenetic processes between COVID-19 and TB, we filtrated the DEGs from transcriptional datasets and identified the common DEGs that cause COVID-19 and TB. From the assessment of the COVID-19 dataset (GES196822), there are 1,668 DEGs, including 839 upregulated DEGs and 829 downregulated DEGs (Supplementary Table S3). Similarly, based on RNA-seq profiling of patients with TB (GSE126614), we identified 779 DEGs, where 470 DEGs were upregulated and 309 DEGs were downregulated (Supplementary Table S4). The summarized information on DEGs for COVID-19 and TB is listed in Table 1. Moreover, there are 96 shared DEGs identified from the COVID-19 and TB datasets by the accomplishment of the cross-comparison evaluation on Jvenn (Figure 2). These results reveal that the 96 common genes screened in this study mediated the regulation of COVID-19 and TB, suggesting that there are some mechanistical commonalities and common pathogenetic processes between COVID-19 and TB.

Analyses of gene ontology and pathway enrichment

To further understand the biological significance and the common signaling pathways of the dataset, we used the common DEGs to implement the GO enrichment approach and pathway enrichment method through EnrichR. For gene ontology analysis, the

top 10 terms related to the biological process, molecular function, and cellular component categories are summarized in Table 2. The bar graph in Figure 3 indicates the comprehensive ontological analysis for each category. Notably, viral genome replication and immune-related pathways are significantly enriched, including negative regulation of viral process (GO:0048525), negative regulation of viral genome replication (GO:0045071), regulation of viral genome replication (GO:0045069), neutrophil activation involved in immune response (GO:0002283), neutrophil-mediated immunity (GO:0002446), defense response to viruses (GO:0051607), and innate immune response (GO:0045087).

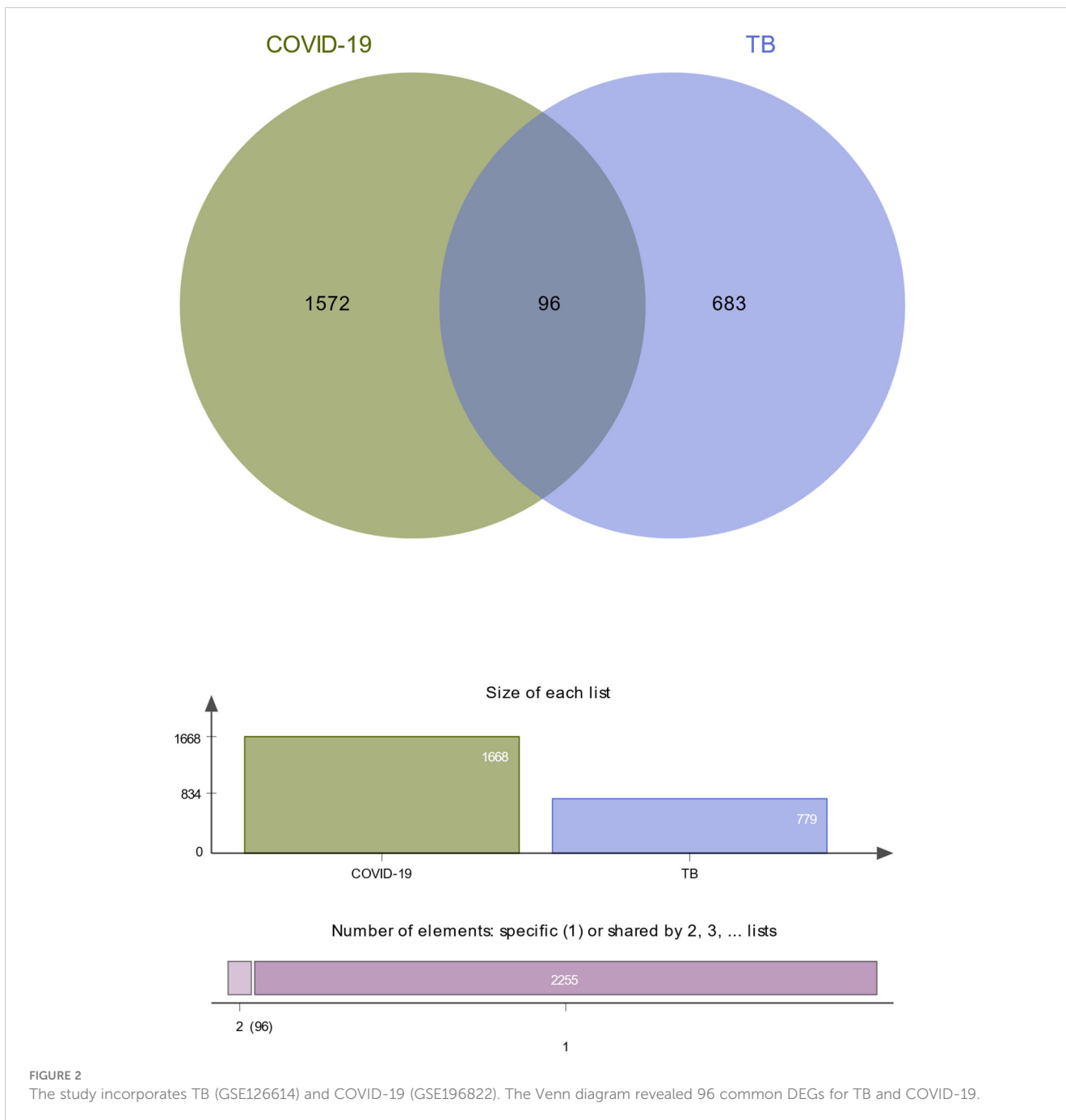
To find the most significant pathways of the mutual DEGs, three global databases were utilized, including Bioplane, KEGG, and WikiPathways. The identified top 10 pathways in the three databases are outlined in Table 3. Moreover, the pathway enrichment study is described in the bar graph in Figure 4. The Bioplane enrichment analysis showed that the common DEGs are mainly involved in the regulation of immune-related pathways, including interferon signaling, interferon alpha/beta signaling, type II interferon signaling (interferon-gamma), interferon-gamma signaling pathway, immune system, antiviral mechanism by interferon-stimulated genes, and interleukin-2 signaling pathway. Furthermore, the KEGG analysis showed the shared DEGs may influence the progression of a variety of infectious diseases, including coronavirus disease, influenza A, measles, hepatitis C, and Epstein–Barr virus infection. Most important of all, the WikiPathways analysis revealed mutual DEGs significantly enriched in the immune response to tuberculosis (WP4197), type I interferon induction and signaling during SARS-CoV-2 infection (WP4868), and host–pathogen interaction of human coronaviruses—interferon induction (WP4880). These results strongly suggest that these mutual DEGs are involved in the occurrence and development of these two infectious diseases through viral genome replication and immune-related pathways.

Protein–protein interaction analysis and hub gene extraction

To identify the interplay and adhesion routes of common DEGs, we analyzed the PPI network constructed from STRING and visualized it in Cytoscape. Figure 5 demonstrates the PPI network of common DEGs, which consists of 176 edges and 49 nodes. As shown, the size and color depth of the circles indicated the degree of intercorrelation of the proteins, and the most prominent nodes are considered the hub genes. From the PPI network analysis utilizing the Cytohubba plugin, 10 hub genes were selected. Figure 6 shows the submodule network of hub-gene connections that consists of 22 nodes and 142 edges. These hub

TABLE 1 Overview of the datasets in this analysis.

Disease name	GEO accession	GEO platform	Total DEG count	Upmodulated DEG count	Downmodulated DEG count
COVID-19	GES196822	GPL20301	1,668	839	829
TB	GSE126614	GPL11154	779	470	309



genes comprised IFI44L, ISG15, MX1, IFI44, OASL, RSAD2, GBP1, OAS1, IFI6, and HERC5, which could be potential biomarkers for common pathogenetic processes between COVID-19 and TB and may accelerate the development of novel therapeutic strategies.

Determination of regulatory networks at the transcriptional level

To investigate the transcriptional regulation of hub genes, a network-based technique was utilized to decipher the regulatory TFs and miRNAs. Figure 7 shows TF regulators interplay with the hub genes, which have 61 nodes and 99 edges. Moreover, Figure 8

depicts the interactions of miRNAs and hub genes, consisting of 29 nodes and 32 edges. From TF-gene and miRNA-gene interaction networks, 61 TFs such as GATA2, FOXC1, USF2, MEF2A, STAT1, SREBF1, POU2F2, and 29 miRNAs such as hsa-mir-26b-5p, hsa-mir-15b-3p, hsa-mir-146a-3p, hsa-mir-34b-3p, hsa-mir-1248, hsa-mir-4256, hsa-mir-3921, and hsa-mir-4653-5p, are discovered.

Identification of candidate drugs

The protein–drug interaction analyses may be useful in drug discovery (Al-Mustanjid et al., 2020). Protein–drug interaction is vital to understanding the function of proteins and discovering

TABLE 2 Ontological analysis of common DEGs between TB and COVID-19.

Category	GO ID	Term	p-value	Genes
GO biological process	GO:0048525	Negative regulation of the viral process	2.96E-14	IFITM3; PARP10; PLSCR1; RSAD2; OAS1; MX1; EIF2AK2; ISG15; PML; OASL; LTF
	GO:0045071	Negative regulation of viral genome replication	8.07E-14	IFITM3; PARP10; PLSCR1; RSAD2; OAS1; MX1; EIF2AK2; ISG15; OASL; LTF
	GO:0140546	Defense response to symbiont	7.55E-13	IFITM3; ZBP1; PLSCR1; RSAD2; OAS1; MX1; IFI6; EIF2AK2; ISG15; RNASE2; IFI44L; OASL
	GO:0045069	Regulation of viral genome replication	7.94E-13	IFITM3; PARP10; PLSCR1; RSAD2; OAS1; MX1; EIF2AK2; ISG15; OASL; LTF
	GO:0043312	Neutrophil degranulation	1.25E-12	TNFAIP6; ANXA3; CRISP3; RNASE3; RETN; OLFM4; MMP8; RNASE2; VNN1; LCN2; OLR1; BPI; S100P; GYG1; CAMP; HSPA1B; CD177; LTF; SIGLEC5
	GO:0002283	Neutrophil activation is involved in the immune response	1.44E-12	TNFAIP6; ANXA3; CRISP3; RNASE3; RETN; OLFM4; MMP8; RNASE2; VNN1; LCN2; OLR1; BPI; S100P; GYG1; CAMP; HSPA1B; CD177; LTF; SIGLEC5
	GO:0002446	Neutrophil-mediated immunity	1.60E-12	TNFAIP6; ANXA3; CRISP3; RNASE3; RETN; OLFM4; MMP8; RNASE2; VNN1; LCN2; OLR1; BPI; S100P; GYG1; CAMP; HSPA1B; CD177; LTF; SIGLEC5
	GO:0051607	Defense response to virus	1.75E-12	IFITM3; ZBP1; PLSCR1; RSAD2; OAS1; MX1; IFI6; EIF2AK2; ISG15; RNASE2; IFI44L; OASL
	GO:0045087	Innate immune response	1.49E-11	IFITM3; CRISP3; MX1; IFI6; ISG15; RNASE3; RNASE2; PML; VNN1; OAS1; LCN2; BPI; APOL1; CAMP; LTF
	GO:0071357	Cellular response to type I interferon	8.44E-10	IFITM3; RSAD2; OAS1; MX1; IFI6; ISG15; IFI35; OASL
GO cellular component	GO:0042581	Specific granule	2.98E-10	ANXA3; CRISP3; LCN2; OLR1; BPI; RETN; OLFM4; MMP8; CAMP; CD177; LTF
	GO:0035580	Specific granule lumen	5.72E-10	CRISP3; LCN2; BPI; RETN; MMP8; OLFM4; CAMP; LTF
	GO:0034774	Secretory granule lumen	3.72E-09	CRISP3; RNASE3; RETN; OLFM4; MMP8; RNASE2; LCN2; SERPING1; BPI; S100P; GYG1; CAMP; LTF
	GO:0070820	Tertiary granule	9.47E-08	TNFAIP6; CRISP3; OLR1; OLFM4; MMP8; CAMP; CD177; LTF; SIGLEC5
	GO:1904724	Tertiary granule lumen	2.50E-07	TNFAIP6; CRISP3; MMP8; OLFM4; CAMP; LTF
	GO:0042582	Azurophil granule	1.03E-04	VNN1; BPI; RNASE3; RETN; OLFM4; RNASE2
	GO:0035578	Azurophil granule lumen	9.29E-04	BPI; RNASE3; RETN; RNASE2
	GO:0005775	Vacuolar lumen	1.08E-03	BPI; RNASE3; RETN; RNASE2; GYG1
	GO:0034364	High-density lipoprotein particle	3.70E-03	CETP; APOL1
	GO:0070821	Tertiary granule membrane	5.23E-03	OLR1; CD177; SIGLEC5
GO molecular function	GO:0003725	Double-stranded RNA binding	4.21E-04	ZBP1; OAS1; EIF2AK2; OASL
	GO:0046914	Transition metal ion binding	1.36E-03	RPH3A; MT2A; PLSCR1; LCN2; TIMM10; MMP8; GYG1; LTF
	GO:0004518	Nuclease activity	3.01E-03	PLSCR1; RNASE3; RNASE2
	GO:0070566	Adenylyltransferase activity	4.95E-03	OAS1; OASL

(Continued)

TABLE 2 Continued

Category	GO ID	Term	p-value	Genes
	GO:0017111	Nucleoside-triphosphatase activity	1.10E-02	GBP6; MX1; RHOH; GBP1; HSPA1B
	GO:0003924	GTPase activity	2.03E-02	GBP6; MX1; RHOH; GBP1
	GO:0008270	Zinc ion binding	2.30E-02	RPH3A; MT2A; PLSCR1; TIMM10; MMP8
	GO:0030283	Testosterone dehydrogenase [NAD(P)] activity	2.38E-02	DHRS9
	GO:0048406	Nerve growth factor binding	2.38E-02	SORT1
	GO:0031721	Hemoglobin alpha binding	2.38E-02	HBD

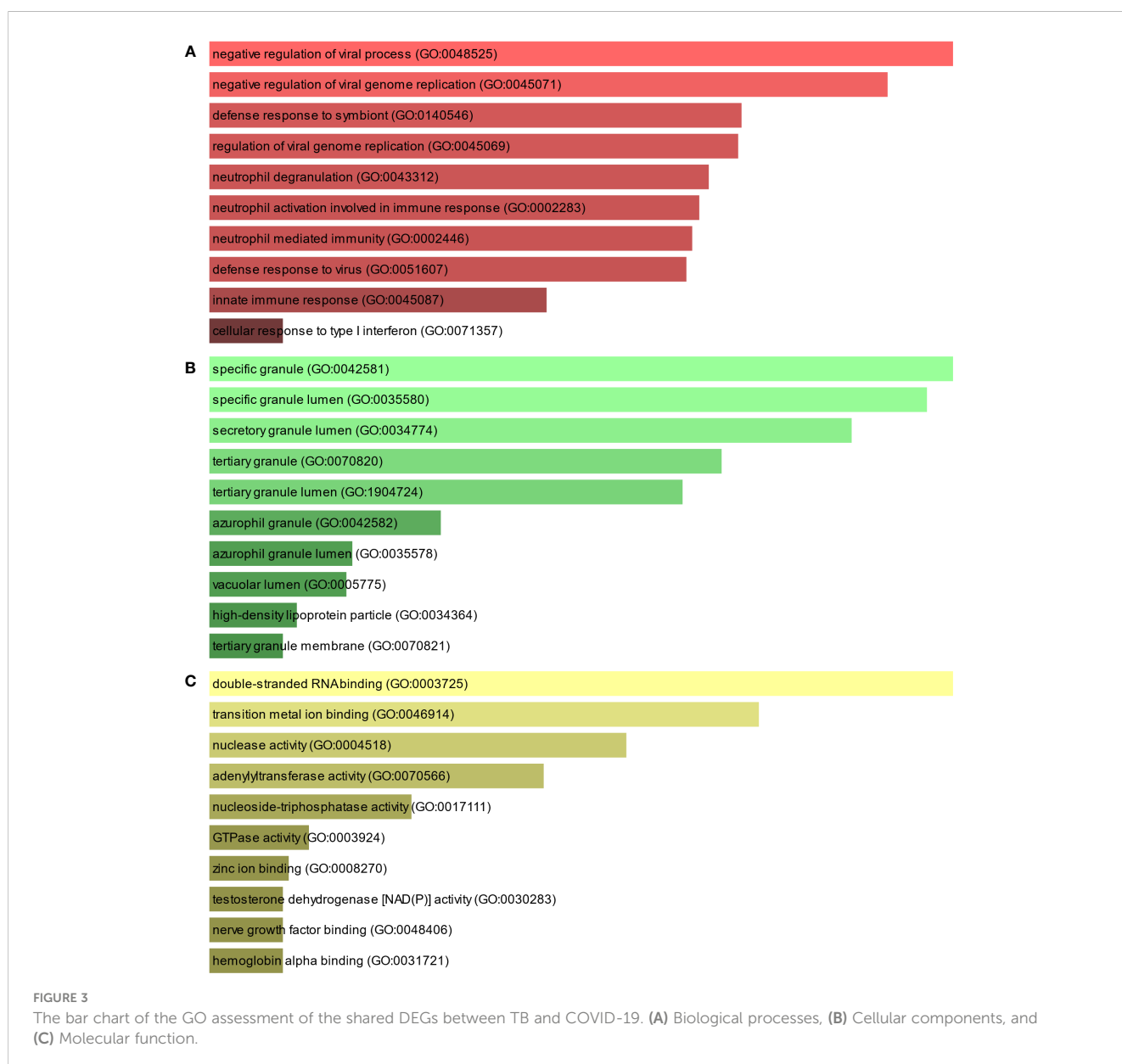


FIGURE 3

The bar chart of the GO assessment of the shared DEGs between TB and COVID-19. (A) Biological processes, (B) Cellular components, and (C) Molecular function.

TABLE 3 Pathway enrichment analysis of common DEGs between TB and COVID-19.

Category	Pathways	p-value	Genes
Bioplanet	Interferon signaling	1.43E-12	IFITM3; GBP6; MX1; IFI6; EIF2AK2; ISG15; IFI35; PML; OASL; HERC5; MT2A; OAS1; GBP1
	Immune system signaling by interferons, interleukins, prolactin, and growth hormones	8.61E-10	IFITM3; GBP6; MX1; IFI6; EIF2AK2; ISG15; IFI35; PML; OASL; HERC5; MT2A; OAS1; GBP1
	Interferon alpha/beta signaling	2.34E-08	IFITM3; OAS1; MX1; IFI6; ISG15; IFI35; OASL
	Type II interferon signaling (interferon-gamma)	4.10E-06	OAS1; IFI6; EIF2AK2; ISG15; GBP1
	Interferon-gamma signaling pathway	7.26E-06	GBP6; MT2A; OAS1; GBP1; PML; OASL
	Immune system	2.02E-05	IFITM3; ZBP1; GBP6; MX1; IFI6; EIF2AK2; ISG15; IFI35; PML; OASL; HERC5; MT2A; OAS1; FBXO6; TLR5; GBP1
	Antiviral mechanism by interferon-stimulated genes	3.59E-04	HERC5; MX1; EIF2AK2; ISG15
	Oncostatin M	3.87E-03	MT2A; OAS1; ANXA3; LCN2; S100P; CAMP
	Interleukin-2 signaling pathway	7.43E-03	IFITM3; MT2A; SMARCD3; IL24; MX1; TBC1D8; IFI44; GBP1; IL18R1; LY6E
	KEGG	Influenza A	1.44E-03
Measles		4.53E-03	OAS1; MX1; EIF2AK2; HSPA1B
Hepatitis C		6.94E-03	RSAD2; OAS1; MX1; EIF2AK2
Cholesterol metabolism		2.41E-02	CETP; SORT1
Coronavirus disease		2.56E-02	OAS1; MX1; EIF2AK2; ISG15
Legionellosis		3.07E-02	TLR5; HSPA1B
Inflammatory bowel disease		3.90E-02	TLR5; IL18R1
Protein processing in the endoplasmic reticulum		4.93E-02	EIF2AK2; FBXO6; HSPA1B
NOD-like receptor signaling pathway		5.66E-02	OAS1; GBP1; CAMP

(Continued)

TABLE 3 Continued

Category	Pathways	p-value	Genes
	Epstein-Barr virus infection	7.34E-02	OAS1; EIF2AK2; ISG15
WikiPathways	Type II interferon signaling (IFNG) WP619	8.85E-07	OAS1; IFI6; EIF2AK2; ISG15; GBP1
	Immune response to tuberculosis WP4197	1.77E-04	OAS1; MX1; IFI35
	Nongenomic actions of 1,25-dihydroxyvitamin D3 WP4341	3.79E-04	RSAD2; ISG15; IFI44L; CAMP
	Type I interferon induction and signaling during SARS-CoV-2 infection WP4868	9.68E-03	OAS1; EIF2AK2
	Host-pathogen interaction of human coronaviruses-interferon induction WP4880	1.09E-02	OAS1; EIF2AK2
	Neural crest cell migration in cancer WP4565	1.81E-02	SORT1; MMP8
	Male infertility WP4673	3.33E-02	EPSTI1; BRCA2; LTF
	p53 transcriptional gene network WP4963	4.12E-02	ISG15; PML
	IL-18 signaling pathway WP4754	4.21E-02	CETP; NRN1; MMP8; IL18R1
	Composition of lipid particles WP3601	4.24E-02	CETP

advancing drugs. Ten possible drug molecules were predicted using EnrichR based on transcriptome characteristics from the DSigDB database, including suloctidil, prenylamine, acetohexamide, terfenadine, prochlorperazine, 3'-azido-3'-deoxythymidine, chlorophyllin, etoposide, clioquinol, and propofol. The 10 potential medications are extracted in accordance with their p-value. Table 4 depicts the potential drugs in the DSigDB database for hub genes. These potential drugs are recommended for the hub genes, a common compound used to treat two diseases.

Discussion

Due to the high incidence and mortality of TB and COVID-19, the main target organ of both is the lung. More importantly, some research recently indicated that there is a strong association

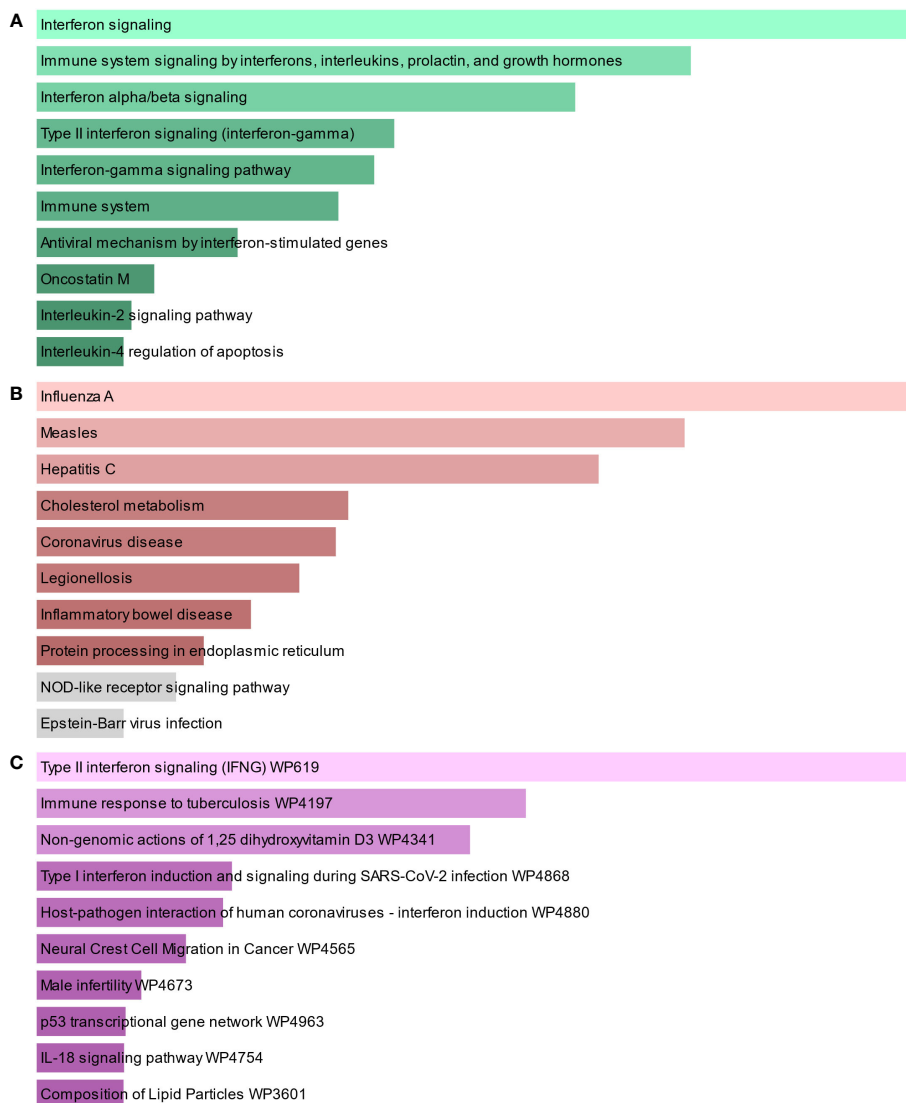


FIGURE 4

The bar graphs of the pathway enrichment of the shared DEGs between TB and COVID-19. (A) Bioplanet, (B) KEGG, and (C) WikiPathways.

between the onset and exacerbation of TB and COVID-19, and likewise, TB is a risk factor for COVID-19 (Fonseca et al., 2021; Gao et al., 2021; Visca et al., 2021). Therefore, it is crucial to explore the common pathogenesis, interaction, and connection between TB and COVID-19.

The enrichment analysis of gene ontology and pathways can help us understand the function and regulation mechanisms of genes in different physiological states. In this study, first of all, 96 common DEGs were identified through the differential analysis of gene expression abundance in transcriptional profiles and the analysis of Venn diagrams, which indicated that there is a certain degree of correlation and similarity between tuberculosis and COVID-19 in their pathogenesis. Subsequently, the functional enrichment analysis of common DEGs was carried out. The results of enrichment analysis showed that these common DEGs were mainly involved in viral genome replication and immune-related pathways. In coronaviruses, the viral genome replication

that evades the immunity system may contribute to the viral process (Perlman and Netland, 2009). The negative regulation of viral genome replication is closely tied to the interferon response pathway, and interferon- γ (IFN- γ) is a genome replication negative regulator of SARS-COV-2 (Bhat et al., 2018; Trugilho et al., 2022). SARS-CoV-2 may trigger aggressive proinflammatory reactions in infected cells, including IL-2, IL1- β , IL-4, IL-6, IL-10, IFN- γ , and tumor necrosis factor- α (TNF- α) (Guan et al., 2020). Furthermore, T-cell depletion caused by *M. tuberculosis* affects host immunity, which increases the body's susceptibility to airborne pathogens, making the host more susceptible to COVID-19 infection (Rahman et al., 2009; Tadolini et al., 2020; Mousquer et al., 2021). In addition, elevated levels of the proinflammatory cytokines IL-6 and TNF- α in COVID-19 patients cause damage to the lymphatic system, resulting in immunosuppression, which contributes to the progression of TB (Tan et al., 2020; Hildebrand et al., 2022).

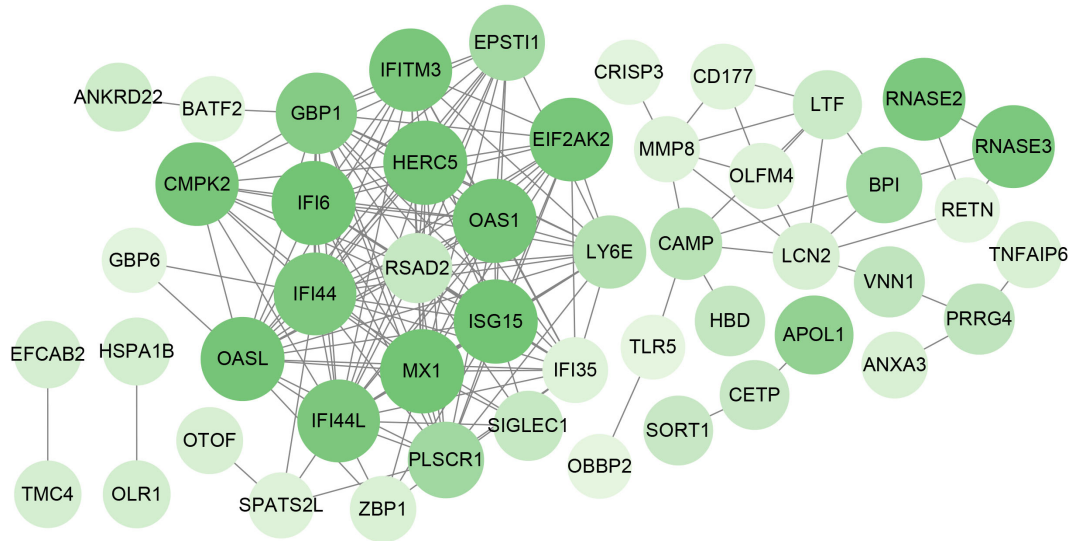


FIGURE 5
 PPI network of the mutual DEGs between COVID-19 and TB. The nodes and the edges of the figure represent DEGs and the interactions between the nodes, respectively. The PPI network contains 176 edges and 49 nodes.

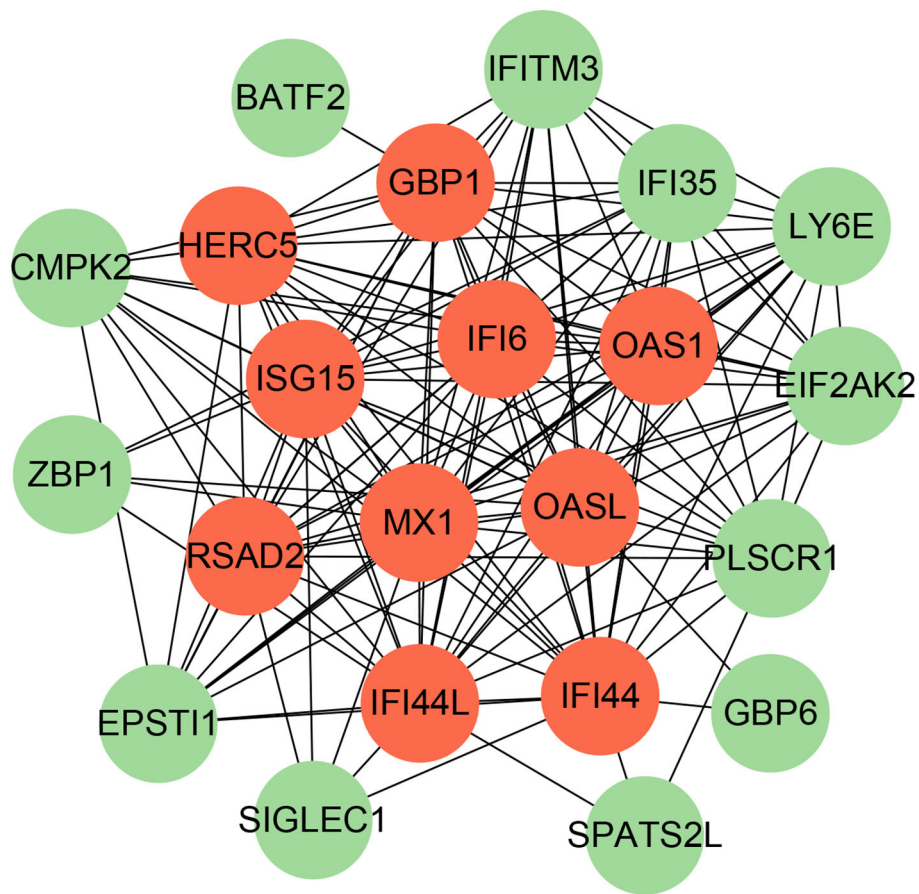


FIGURE 6
 The PPI network from all the shared DEGs is constructed by the Cytohubba plugin in Cytoscape. Red nodes present the selected top 10 hub genes. The network has 22 nodes and 142 edges.

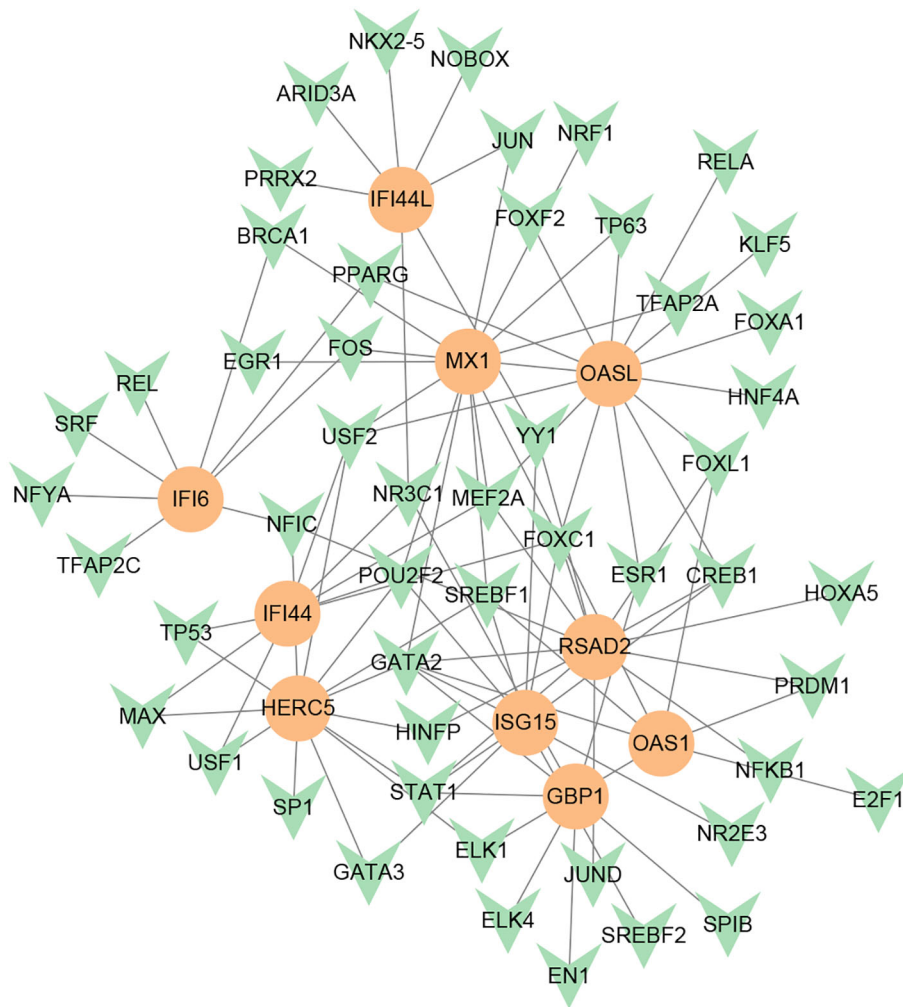


FIGURE 7

DEG-TF interaction network created by the NetworkAnalyst. The orange nodes represent gene symbols interacting with TFs, while the herringbone nodes represent TFs.

The shared DEGs are utilized to construct the PPI network, in which the hub gene is the most significant regulator in the common pathogenetic processes of TB and COVID-19. IFI44L is a potential target for reducing viral replication (Dediego et al., 2019). IFI44L promotes positive regulation and eliminates *M. tuberculosis* from human macrophages, highlighting its potential as a therapeutic target against *M. tuberculosis* infection (Jiang et al., 2021; Deng et al., 2023). IFI44 and IFI44L are antiproliferative factors that independently limit respiratory syncytial virus (RSV) infection (Busse et al., 2020). The expression levels of IFI44L and antiviral genes exhibit alterations during SARS-CoV-2 infection in various human cells, such as liver, respiratory epithelial, and stomach cells (Geerling et al., 2022). IFI44 is situated on human chromosome 1p31.1 and is part of the interferon-stimulated gene (ISG) family, which has a crucial function in regulating immunity and recognizing tumor cells (Lukhele et al., 2019; Boutin et al., 2021; Li et al., 2021a; Li et al., 2021b). IFI44 negatively regulates the IFN signaling pathway, promotes viral replication and bacterial proliferation, and is a crucial molecular target for immune evasion by SARS-CoV-2 (Zheng et al., 2022). Although ISG15 antiviral does not directly hinder the viral life cycle, it restricts viral transmission by

joining the host response to modify the immune-metabolic network and restrain the availability of resources for viral amplification (Raso et al., 2020; Gold et al., 2022; Munnur et al., 2022). ISG15 can collaborate with IL-12 to stimulate T and NK cells to produce IFN- γ , which regulates *Mycobacterium tuberculosis* infection through an extracellular cytokine-like pathway (Bogunovic et al., 2012; Kimmey et al., 2017). Mx1 has noteworthy antiviral effects on hematopoietic cells, alongside its recognized antiviral activity on nonhematopoietic cells (Spitaels et al., 2019; Gough et al., 2022). OASL induces amyloid fibrillation in RIPK3, promoting virus-induced necrosis (Lee et al., 2023). OASL is strongly induced upon viral infection to enhance the antiviral IFN response (Leisching et al., 2017; Ghosh et al., 2019). The association between OASL and TB infection has also been validated, and OASL plays a central role in COVID-19 immunopathogenesis (Zhang et al., 2019; Hasankhani et al., 2021; Yi et al., 2021). RSAD2 is the direct suppressor of viral replication and facilitates TLR9- and TLR7-mediated production of IFN- α (Mantovani et al., 2022). The adaptive behavior of NK cells during viral infection is facilitated through STAT1-mediated epigenetic control of RSAD2 (Wiedemann et al., 2020). GBP1 was found to be one of the potential biomarkers of

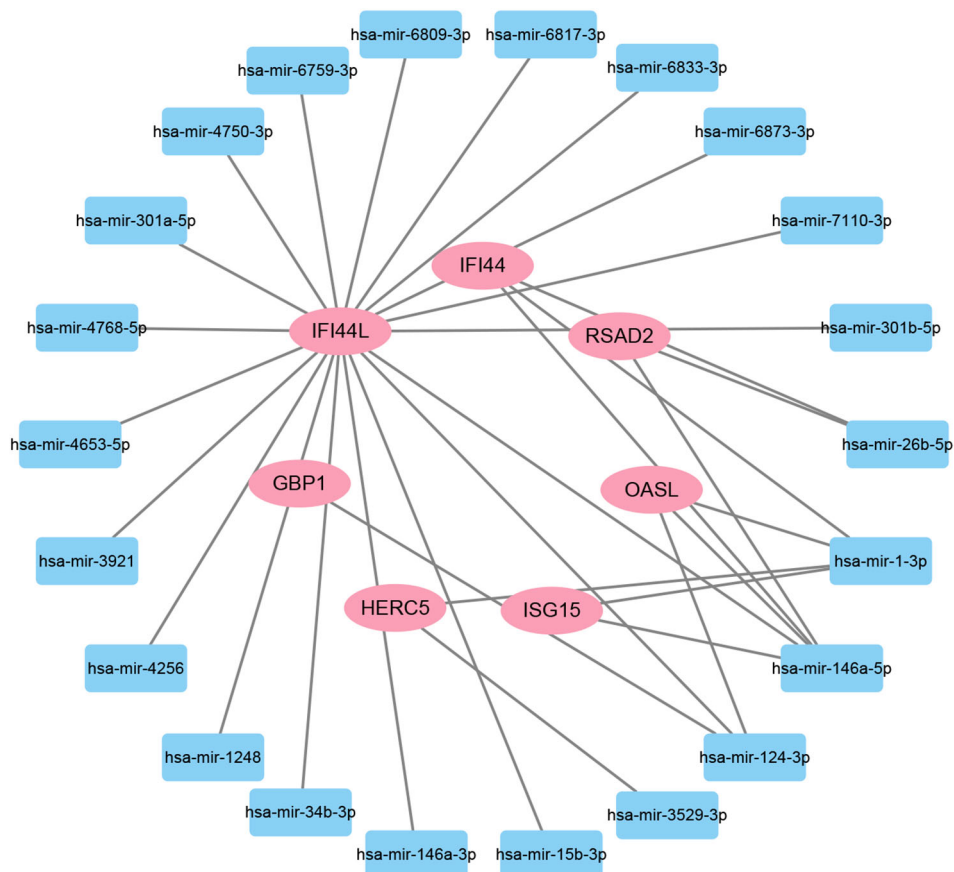


FIGURE 8

The regulatory interaction network of DEG-miRNAs. MiRNAs are presented by the square node, and gene symbols interacting with miRNAs are in an oval shape.

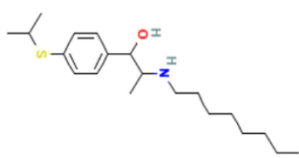
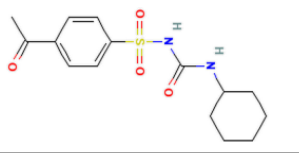
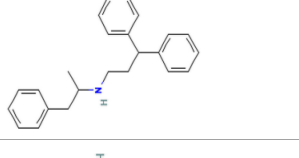
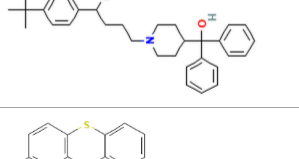
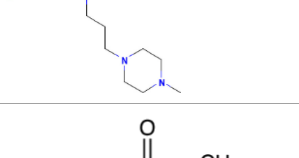
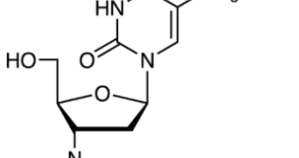
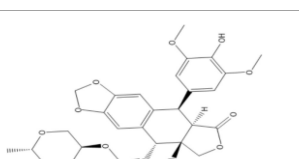
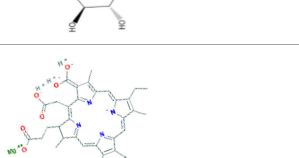
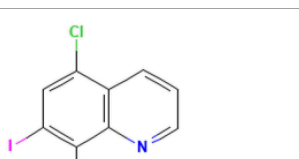
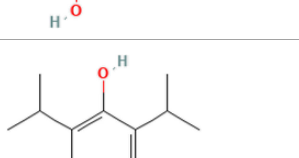
active TB, and its expression was negatively correlated with lymphocyte activity but positively correlated with myeloid and inflammatory cell activity (Perumal et al., 2020; Chen et al., 2022). In severe conditions of COVID-19, there is a high abundance of CXCL10+ and CCL2+ inflammatory macrophages that heavily express the GBP1 inflammatory gene (Zhang et al., 2020). OAS1 acts as a negative regulator of the expression of chemokines and interferon-responsive genes in human macrophages (Lee et al., 2019). Reduced OAS1 expression due to a common haplotype is proven to be related to the severity of COVID-19 (Banday et al., 2022). Genetically regulated loss of OAS1 expression contributes to impaired spontaneous clearance of SARS-CoV-2 and an increased risk of hospitalization for COVID-19 (Banday et al., 2021; Huffman et al., 2022). Compared to normal tissues, IFI6 is markedly upregulated in white blood cells from COVID-19 patients and nasopharyngeal tissues infected with SARS-CoV-2 and is associated with antiviral immune modulation and clinical progression (Dong et al., 2022; Sun et al., 2023; Villamayor et al., 2023). The antiviral activity displayed by HERC5 makes them promising drug targets for the development of novel antiviral therapeutics that can augment the host antiviral response (Jacquet et al., 2020; Mathieu et al., 2021).

TFs and miRNAs that act as upstream regulators of these hub genes have also been discovered to better understand the pathological basis of these disease states. Transcription factor

GATA2 is associated with hematopoietic dysfunction in severe COVID-19 patients (Wang et al., 2021). Downregulation of GATA2, involved in lymphocyte commitment, is also found in TB (Li et al., 2023). The phosphorylation of STAT1 was reportedly strengthened in severe COVID-19 cases that failed to induce transcription of interferon-stimulated response elements (ISRE) by unbalanced JAK/STAT signaling (Rincon-Arevalo et al., 2022). MiR-26b-5p targeted cyclooxygenase 2 (COX2), leading to a decrease in its expression. Consequently, there were considerable reductions in the levels of proinflammatory mediators such as prostaglandin E2 (PGE2), TNF- α , and IL-6 in retinal artery and human dermal microvascular endothelial cells (HMEC-1). This resulted in an effective inhibition of inflammation (Jiang et al., 2020). MiR-26b-5p was predicted to be regulated by spike, ACE, and histone deacetylation (HDAC) pathways in COVID-19 (Teodori et al., 2020). Although many previous studies have suggested that these TFs and miRNAs may have potential therapeutic effects, these analytical results require further experiments to confirm their effectiveness and authenticity.

Drugs tending to regulate the hub genes were identified from the DSigDB database. The hub genes, which act as regulators of the common pathogenic processes of both diseases and can lead to the simultaneous administration of antiviral and anti-TB drugs, have the potential to provide significant clinical benefit to this

TABLE 4 Potential drugs for COVID-19 and TB.

Name	<i>p</i> -value	Chemical formula	Structure
Suloctidil HL60 UP	2.19E-22	C ₂₀ H ₃₅ NOS	
prenylamine HL60 UP	3.45E-21	C ₂₄ H ₂₇ N	
Acetohexamide PC3 UP	1.15E-19	C ₁₅ H ₂₀ N ₂ O ₄ S	
Terfenadine HL60 UP	1.17E-13	C ₃₂ H ₄₁ NO ₂	
Prochlorperazine MCF7 UP	4.28E-11	C ₂₀ H ₂₄ ClN ₃ S	
3'-Azido-3'-deoxythymidine CTD 00007047	8.64E-11	C ₁₀ H ₁₃ N ₅ O ₄	
Chlorophyllin CTD 00000324	8.57E-10	C ₃₄ H ₃₄ MgN ₄ O ₆	
Etoposide HL60 UP	4.90E-09	C ₂₉ H ₃₂ O ₁₃	
Clioquinol PC3 UP	6.60E-09	C ₉ H ₅ ClNO	
Propofol MCF7 UP	9.84E-09	C ₁₂ H ₁₈ O	

patient population. Some of the drugs identified in this study are proposed by different authors as therapeutics for the treatment of COVID-19 or TB, for example, (1) suloctidil is found to be one of the candidate drugs between COVID-19 and idiopathic pulmonary fibrosis (Chen et al., 2022); (2) acetoexamide is a nucleotide-binding domain (NBD)-binding drug that can be used against COVID-19 by preventing replication and viral attachment to the cell surface binding immunoglobulin protein (csBiP) (Zhang et al., 2021); (3) The use of prochlorperazine has been shown to decrease the replication ability of SARS-CoV-2, which is linked to the ACE2 receptor. Also, prochlorperazine is found significant inhibition in lung pathology and lung viral load of SARS-CoV-2-challenged hamsters. Prochlorperazine can bind to G-quadruplexes (G4s), a secondary structure in nucleic acids that is known to impact numerous cellular processes, including viral replication and transcription. This binding can impede SARS-CoV-2 reverse transcription and ultimately reduce the lung viral load (Roy et al., 2023). (4) The application of chlorophyllin and molnupiravir as a specific antiviral drug for SARS-CoV-2 can diminish the detrimental genetic alterations and host cell harm caused by molnupiravir while enhancing the therapeutic effectiveness (Clark et al., 2022).

While the genes we have identified offer fresh perspectives on the creation of potential therapeutic targets for COVID-19 and TB, the validation of these gene targets and drugs requires continued investigation through experimental studies like cellular and animal models. Also, information and methodological biases preclude the full reproduction of potential genetic links using computational biology techniques. Additionally, translating experimental results into clinical applications remains a significant challenge. These are the main limitations of our current study and the focus of our future research.

Conclusion

To help get insights into the common pathogenetic processes between the SARS-CoV2 infection and TB, we utilized transcriptomic data analysis to determine the shared pathways and biomarkers in TB and COVID-19. There are 96 common DEGs of TB and COVID-19 identified by bioinformatics tools. GO terms and signaling pathway enrichment analysis revealed that 96 common DEGs were mainly involved in the regulation of viral genome replication and immune-related pathways. Moreover, through the PPI analysis of DEGs, the top 10 hub genes were extracted, including IFI44L, ISG15, MX1, IFI44, OASL, RSAD2, GBP1, OAS1, IFI6, and HERC5, which may be a therapeutic target for COVID-19 and help to find drug molecules and drug-target interactions. Also, gene-TF and gene-miRNA association were examined to gain a deeper understanding of COVID-19 progression. In addition, several potential drugs were listed for COVID-19 patients with TB treatment, including suloctidil, prenylamine, acetoexamide, terfenadine, prochlorperazine, 3'-azido-3'-deoxythymidine, chlorophyllin, etoposide, clioquinol, and propofol. We hope these findings may provide key perspectives for developing novel and effective medications to combat COVID-19 and TB.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#). Further inquiries can be directed to the corresponding authors.

Author contributions

TH: Data curation, Methodology, Supervision, Writing – original draft. JH: Investigation, Supervision, Writing – original draft. XZ: Conceptualization, Project administration, Writing – review & editing. HP: Visualization, Writing – review & editing. FH: Investigation, Writing – review & editing. AD: Project administration, Writing – review & editing. BY: Conceptualization, Writing – original draft. NJ: Conceptualization, Writing – original draft. XL: Project administration, Writing – review & editing. KY: Methodology, Writing – review & editing. ZW: Investigation, Project administration, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcimb.2023.1280223/full#supplementary-material>

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SUPPLEMENTARY TABLE 1

The baseline characteristic of sample in COVID-19 (GSE196822).

SUPPLEMENTARY TABLE 2

The baseline characteristic of sample in TB (GSE126614).

SUPPLEMENTARY TABLE 3

The differential analysis matrix of COVID-19.

SUPPLEMENTARY TABLE 4

The differential analysis matrix of TB.

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