Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Differential Expression of IFI16, IL-33 and CD55 Link Potential Common Pathogenic Mechanisms for COVID-19 and Ulcerative Colitis

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Background: The Coronavirus disease 2019 (COVID-19) pandemic has significantly impacted global health and shares several clinical features with ulcerative colitis (UC). However, the existence of a common pathological mechanism between COVID-19 and UC remains uncertain. Additionally, effective treatment strategies for UC patients infected with COVID-19 are not well established. In this study, we investigate the potential shared pathogenesis of UC and COVID-19 and explore possible therapeutic regimens through bioinformatics and systems biology approaches.

Methods: Common differentially expressed genes (DEGs) were extracted from the COVID-19 and ulcerative colitis (UC) datasets for functional enrichment, pathway analysis. The EnrichR database was used to predict potential transcription factors (TFs), microRNAs (miRNAs), and related drugs and diseases, enabling the construction of a regulatory network for both conditions.

Results: We identified 115 significant common DEGs, with 11 high-confidence hub genes—including IFI16, IL-33, and CD55—implicated in innate immunity and inflammatory regulation. Pathway analysis revealed enrichment in interferon signaling, neutrophil activation, and cytokine-mediated responses. Regulatory network reconstruction highlighted miR-155-5p and transcription factors (eg, STAT1) as key regulators. Drug repurposing efforts prioritized retinoic acid, cyclosporine, and TD-139, which target these shared mechanisms.

Conclusion: This study reveals robust molecular commonalities between COVID-19 and UC, highlighting dysregulated immune pathways and regulatory networks as shared mechanisms. We propose novel drug-repurposing candidates supported by network-based evidence, offering potential therapeutic strategies for patients with comorbid COVID-19 and UC.

Keywords: ulcerative colitis, COVID-19, GEO database, protein-protein interaction network, bioinformatics

Introduction

The novel coronavirus pneumonia, also known as the novel coronavirus pneumonia, The subsequent global pandemic has evolved into a profound health crisis,[1] with 776,546,006 confirmed cases of COVID-19 globally as of 19–10,2024. 7,070,128 deaths (https://covid19.who.int). Although COVID-19 primarily presents as a respiratory disease, recent scientific evidence suggests that it may also be implicated in several gastrointestinal disorders, particularly inflammatory bowel disease (IBD).[2] Among these complications, ulcerative colitis (UC) has garnered significant attention due to the complex interactions between viral infection and immune dysregulation, highlighting the need for further investigation into the potential impact of SARS-CoV-2 on patients with IBD.[3]

Ulcerative colitis (UC) is a chronic autoimmune disorder causing inflammation and ulceration of the colonic and rectal mucosa[4,5] The prevalence of UC is approximately 40 to 300 per 100,000 persons, depending on geographic region

Received: 28 May 2025
Accepted: 8 December 2025
Published: 17 December 2025

and population demographics.[6] Many patients require ongoing treatment with nonsteroidal anti-inflammatory drugs, immunosuppressants, or biologic agents to manage their condition.[7]

Numerous clinical features of COVID-19 resemble those in ulcerative colitis (UC), including dysregulated inflammatory responses, tissue injury, and immune dysfunction.[8] Recent research underscores a notable correlation between viral infections and the exacerbation of UC, particularly indicating that SARS-CoV-2 may worsen the disease and affect clinical outcomes.[9] Furthermore, patients with UC face a higher risk of severe illness and hospitalization due to COVID-19 compared to the general population.[10] Additionally, the immunomodulatory effects of SARS-CoV-2, including cytokine storms and lymphocyte depletion, may disrupt the intestinal environment and intensify gut inflammation.[2] Moreover, the lack of effective and safe therapies for COVID-19, especially in patients with concurrent UC, poses significant challenges for care.

In this study, we employed an integrative bioinformatics approach to systematically investigate shared gene expression patterns, regulatory networks, and functional pathways that may underlie the comorbidity of COVID-19 and ulcerative colitis (UC). Using multi-source transcriptomic data obtained from peripheral blood and diseased tissue samples, we sought to: identify consistently dysregulated genes and high-confidence hub genes with mechanistic relevance; decipher the roles of transcription factors, miRNAs, and signaling pathways in mediating shared immunopathological processes; and propose novel therapeutic candidates through network-based drug repurposing strategies aimed at these convergent mechanisms. This analysis builds upon prior evidence—such as the upregulation of IL23 which has been implicated in both autoimmune-driven inflammation and antiviral responses—to establish a molecular foundation linking COVID-19 and UC.[11,12] Ultimately, this work aims to provide deeper mechanistic insights into the interplay between these conditions and to facilitate the development of targeted therapies for affected patients.

Methods

Data Acquisition

In this study, transcriptome data were obtained from peripheral blood samples of patients with COVID-19 and ulcerative colitis (UC) through the GEO database platform.[13] Specifically, we utilized the COVID-19 dataset with GEO accession ID GSE179850, which included 16 samples from patients who tested negative for COVID-19 and 31 samples from those who tested positive, following the removal of any duplicate entries. For the UC patient data, we incorporated results from two databases: GSE38713, which comprised transcriptomic data from 30 UC patients and 13 healthy controls, and GSE92415, which included data from 162 UC patients and 21 healthy individuals.

Identification of Common Differentially Expressed Genes (DEGs)

Differentially expressed genes (DEGs) were identified from one COVID-19 dataset and two ulcerative colitis (UC) datasets using R software (version 4.0.2). Raw count data were processed and normalized using the DESeq2 package to account for library size and composition biases. The statistical testing for differential expression was performed using the Wald test implemented in DESeq2, which generates p-values by comparing the estimated coefficient to its standard error under the negative binomial generalized linear model.

To minimize the impact of potential confounders, the model included adjustments for key batch effects and biological covariates. Multiple testing correction was applied using the Benjamini-Hochberg false discovery rate (FDR) method to control the proportion of false positives among significantly called genes. Genes with $|\log2FoldChange| \geq 1.0$ and adjusted p-value < 0.05 were considered statistically significant DEGs.

To identify common DEGs across datasets, the "VennDiagram" package in R was utilized. Specifically, common DEGs present in at least two of the three datasets were extracted for further functional analysis.

GO and KEGG Enrichment Analysis

We conducted Gene Ontology (GO) enrichment and KEGG pathway analysis using the "clusterProfiler" package in R.[14] For GO analysis, a total of 115 differentially expressed genes (DEGs) were input into the enrichment analysis. Statistical significance of enrichment was determined using a hypergeometric test, with multiple testing correction applied via the

Benjamini-Hochberg false discovery rate (FDR) method. Only terms with an adjusted p-value < 0.05 and an enrichment score (calculated as -log10(adjusted p-value)) > 1.3 (equivalent to FDR < 5%) were considered significantly enriched. The top five functional terms from the biological process (BP), cellular component (CC), and molecular function (MF) categories were prioritized based on comprehensive scores. For KEGG pathway analysis, we applied identical statistical thresholds and selected two most significantly enriched pathways (adjusted p-value < 0.05) that were also biologically relevant to our study context. Data from the MSigDB Collections gene sets database (https://www.gsea-msigdb.org/gsea/msigdb/index.jsp) supported these analyses, aiding further investigation of gene functions and pathways.

Protein-Protein Interaction (PPI) Analysis

Protein-protein interaction (PPI) analysis of PPI networks is essential for investigating biological processes and elucidating protein interactions, thereby enhancing our understanding of underlying molecular mechanisms and functions.[15] We utilized STRING version 11.0 (https://cn.string-db.org/) to analyze 115 differentially expressed genes, constructing a PPI network with a median confidence score of 0.7. Visualization of the network was performed using Cytoscape version 3.7.2.[16] In this visualization, the size and color of the nodes represent the topological analysis scores of the genes, facilitating a clearer interpretation of the biological processes and protein interactions involved.

Extraction of Hub Genes

CytoHubba, a Cytoscape plugin, employs various network indicators to identify key regulators in biological networks, enhancing our understanding of complex processes. In this study, we used CytoHubba (https://apps.cytoscape.org/apps/cytohubba) to screen the PPI network module for critical hub gene. By applying DMCC, MCC, and MNC methods, we identified the top 20 genes and cross-referenced the results to isolate 11 core hub genes. Their importance was visually represented using a red-to-yellow color gradient. Finally, we conducted ROC analysis with the pROC package (version 1.18.0) in R (version 4.2.1). In this analysis, the predictor variable was the expression level of each individual candidate gene, and the outcome variable was the binary classification of sample status. We assessed the diagnostic performance of each gene by calculating the Area Under the Curve (AUC) with 95% confidence intervals using DeLong's method. The results were visualized using the ggplot2 package (version 3.3.6).

Prediction of Transcription Factors and miRNAs

We utilized the online tool Enrichr (https://maayanlab.cloud/Enrichr/), an open web server that integrates extensive resources for gene set enrichment analysis, providing a user-friendly analysis platform.[16] We imported commonly differentially expressed genes into Enrichr and identified 136 associated transcription factors (TFs) that regulate chromatin and transcription by recognizing specific DNA sequences.[17] Additionally, to better understand the interactions between genes and miRNAs, we conducted in-depth analyses using the miRTarBase module of Enrichr. For further screening, we selected the top 10 TFs based on their combined scores and visualized their interactive networks using Cytoscape software. Based on the common differentially expressed genes, a total of 1492 miRNAs were predicted. For further screening, we selected the top 10 miRNAs based on their combined scores and visualized their interactive networks using Cytoscape software. As a leading miRNA-target interaction database, miRTarBase provided valuable data support for our analyses.[18]

Identification of Potential Drug Candidates

We employed the DSigDB module of the Enrichr platform,[19] to analyze differentially expressed genes, facilitating the identification of potential therapeutic drugs by accurately linking gene sets to UC pathogenesis.

Gene-Disease Association Analysis

Utilizing the DisGeNET database,[20] which integrates extensive data on genes, variants, and their relationships to human diseases, we conducted a systematic analysis of core genes and their associations with diseases and comorbidities using Cytoscape software to enhance our understanding of disease pathogenesis.

Results

Exploring Differentially Expressed Genes in COVID-19 and UC

Identification of common differentially expressed genes (DEGs) between ulcerative colitis and COVID-19 is crucial for elucidating the relationship and potential interactions between these two conditions. This study outlines all the key steps taken in this analysis (Figure 1). We downloaded datasets related to ulcerative colitis (UC) and COVID-19 from the Gene Expression Omnibus (GEO), specifically two datasets for ulcerative colitis and one for novel coronavirus pneumonia. A total of 12,003 differential genes were identified in the COVID-19 dataset, while 797 and 966 DEGs were screened from the ulcerative colitis datasets GSE38731 and GSE92415, respectively. By intersecting the differentially expressed genes across the three datasets, we obtained 115 common DEGs (Figure 2A). We further characterized these 115 common DEGs using a volcano plot (Figure 2B), which displays the magnitude of expression change against the statistical significance for each gene. This analysis confirmed a clear separation between significantly upregulated and downregulated genes. The distinct upregulation and downregulation patterns of these common DEGs not only suggest their critical roles in the underlying pathophysiology but also reveal a high degree of consistency, indicating potential interconnected mechanisms between ulcerative colitis and COVID-19.

Functional Enrichment Analysis of Common DEGs

We performed Gene Ontology (GO) and KEGG enrichment analyses to explore the biological roles of common differentially expressed genes (DEGs), as shown in Figure 3A(Bubble size is proportional to the strength of the correlation). The GO analysis is categorized into three independent domains: Biological Process (BP), describing

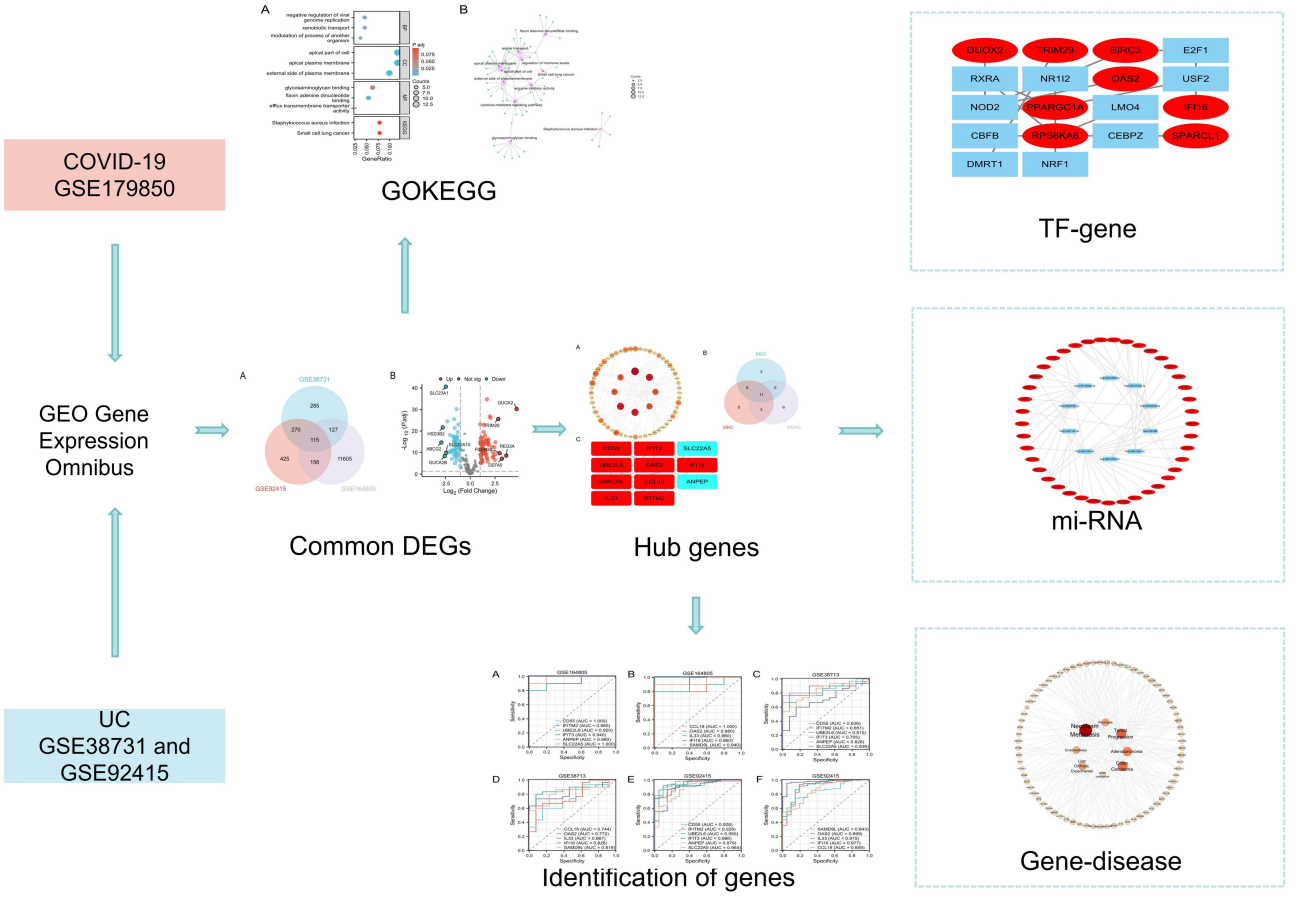

Figure 1 Workflow for identifying shared mechanisms between UC and COVID-19. The chart outlines the process of identifying common differentially expressed genes (DEGs) from ulcerative colitis (UC) and COVID-19 datasets, followed by comprehensive functional and network analyses including TF-gene, miRNA, drug, and disease interactions.

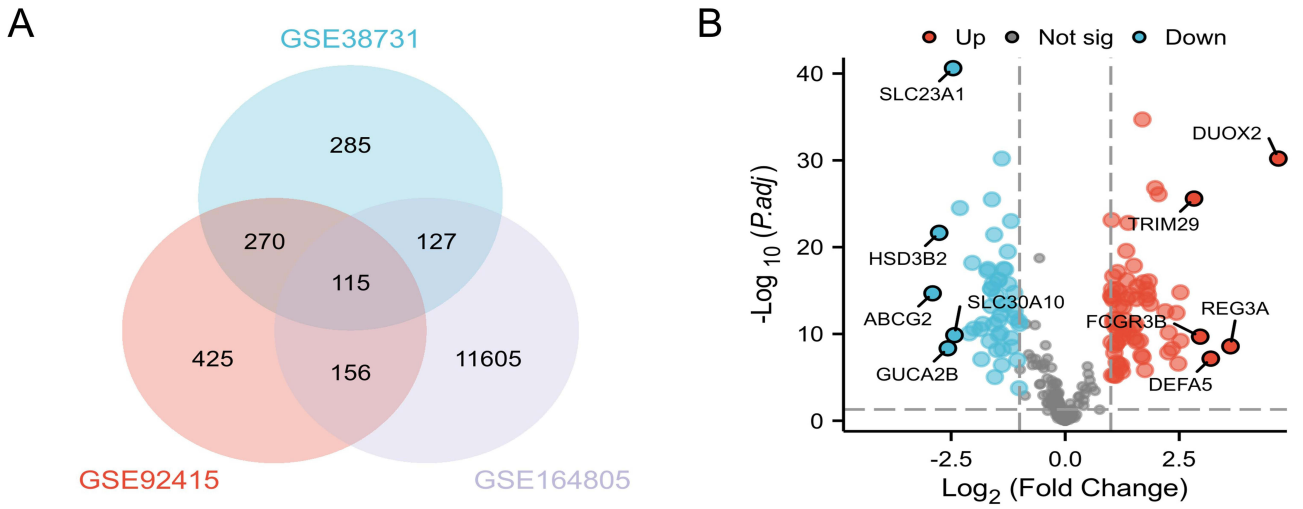

Figure 2 Venn and Volcano Plots of Common Differentially Expressed Genes. (**A**) Venn diagram illustrating the overlap of common differentially expressed genes (|log2FoldChange| ≥ 1.0 and |adj. p-value| < 0.05). (**B**) Volcano Plots of Common Differentially Expressed Genes.

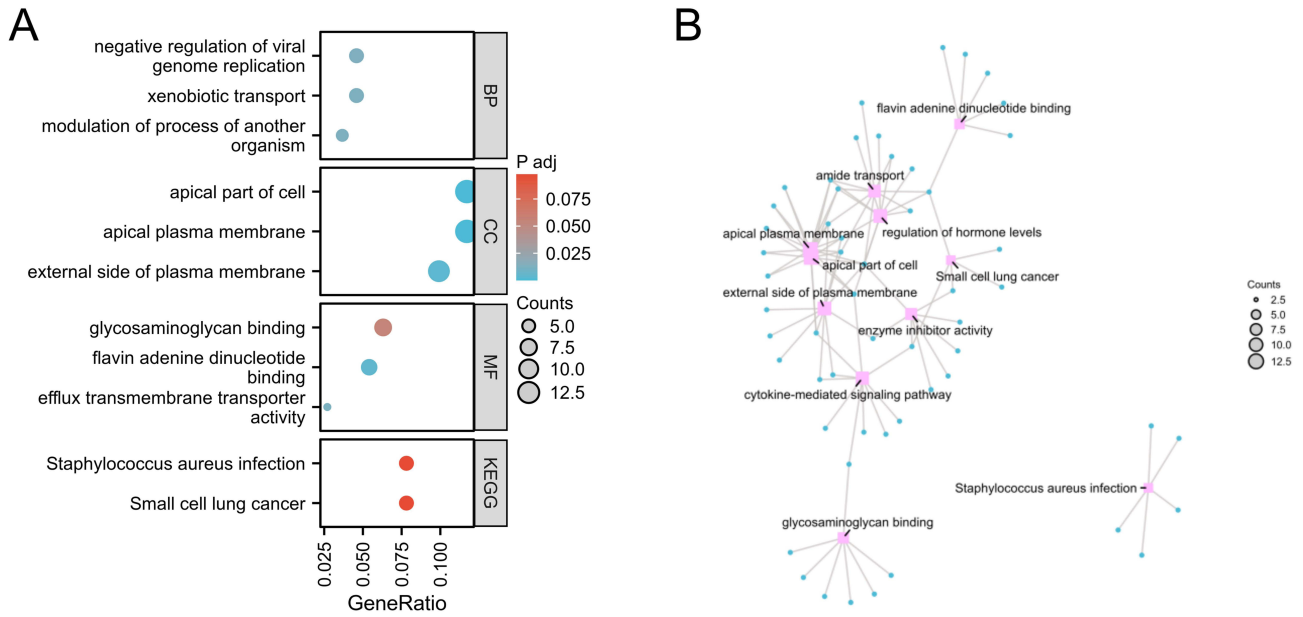

Figure 3 GO and KEGG functional enrichment analysis of the DEGs between COVID-19 and UC. (**A**) Functional enrichment analysis of differentially expressed genes. Bar plots display significantly enriched Gene Ontology (GO) terms and KEGG pathways in biological process (BP), cellular component (CC), molecular function (MF), and KEGG categories. Bar length represents the gene ratio; point size indicates the number of genes per term, and color corresponds to the adjusted p-value. Key enriched terms include regulation of hormone levels, granulocyte chemotaxis, glycosaminoglycan binding, and Staphylococcus aureus infection pathway. (**B**) Network of functional enrichment associations. The network illustrates relationships among significantly enriched GO terms and pathways. Node size reflects the number of genes associated with each term. Edges represent functional similarity or co-occurrence between terms. Representative terms include small cell lung cancer, Staphylococcus aureus infection, and glycosaminoglycan binding.

coordinated biological events or objectives; Cellular Component (CC), describing the specific locations within a cell where gene products are active; and Molecular Function (MF), describing the precise biochemical activities at the molecular level. Additionally, KEGG pathway analysis was performed to identify significant biological pathways in which the genes are involved, providing a systems-level perspective on their functions. For identifying significant functional items and pathways, a threshold of p-value < 0.25 and padjust < 0.05 was applied. The results highlighted significant enrichment in biological processes related to hormone regulation, cytokine signaling, amide transport, microbe degradation, and granulocyte chemotaxis. Cellular component enrichment was noted in the apical cell region,

https://doi.org/10.2147/JMDH.S543183

apical plasma membrane, outer plasma membrane, collagen-rich extracellular matrix, and cell-cell junctions. Notable molecular functions included enzyme inhibitor activity, glycosaminoglycan binding, and transmembrane transporter activity. KEGG analysis identified key pathways associated with common DEGs, such as Staphylococcus aureus infection and small cell lung cancer. Network maps were constructed to visualize the top three results from BP, CC, MF, and KEGG analyses (Figure 3B), this network moves beyond a simple listing of results to model the functional ecosystem defined by our gene set, highlighting the collaborative roles of genes across different ontological layers and pathways.

PPI Network and Hub Genes of Common DEGs

We utilized the STRING database to construct a protein-protein interaction (PPI) network between COVID-19 and differentially expressed genes (DEGs) in primary sclerosing cholangitis (PSC), visualized using Cytoscape software (Figure 4A). This PPI network comprised 64 nodes and 106 edges. To identify key hub genes, we performed Degree analysis with the CytoHubba tool, employing the DMCC, MCC, and MNC algorithms, and selected the top 20 intersecting genes (Figure 4B). Eleven hub genes were identified: IFI16, UBE2L6, OAS2, IFIT3, SAMD9L, IFITM2, ANPEP, IL33, CD55, CCL18, and SLC22A5 (Figure 4C). Among these, SLC22A5 and ANPEP were down-regulated, while the remaining nine genes were up-regulated. ROC analysis performed on whole-blood RNA expression data from COVID-19 and UC patients showed that all 11 hub genes achieved AUC values above 0.7 (range: 0.72–0.89), suggesting moderate to strong discriminatory capacity between disease and control groups within peripheral blood samples

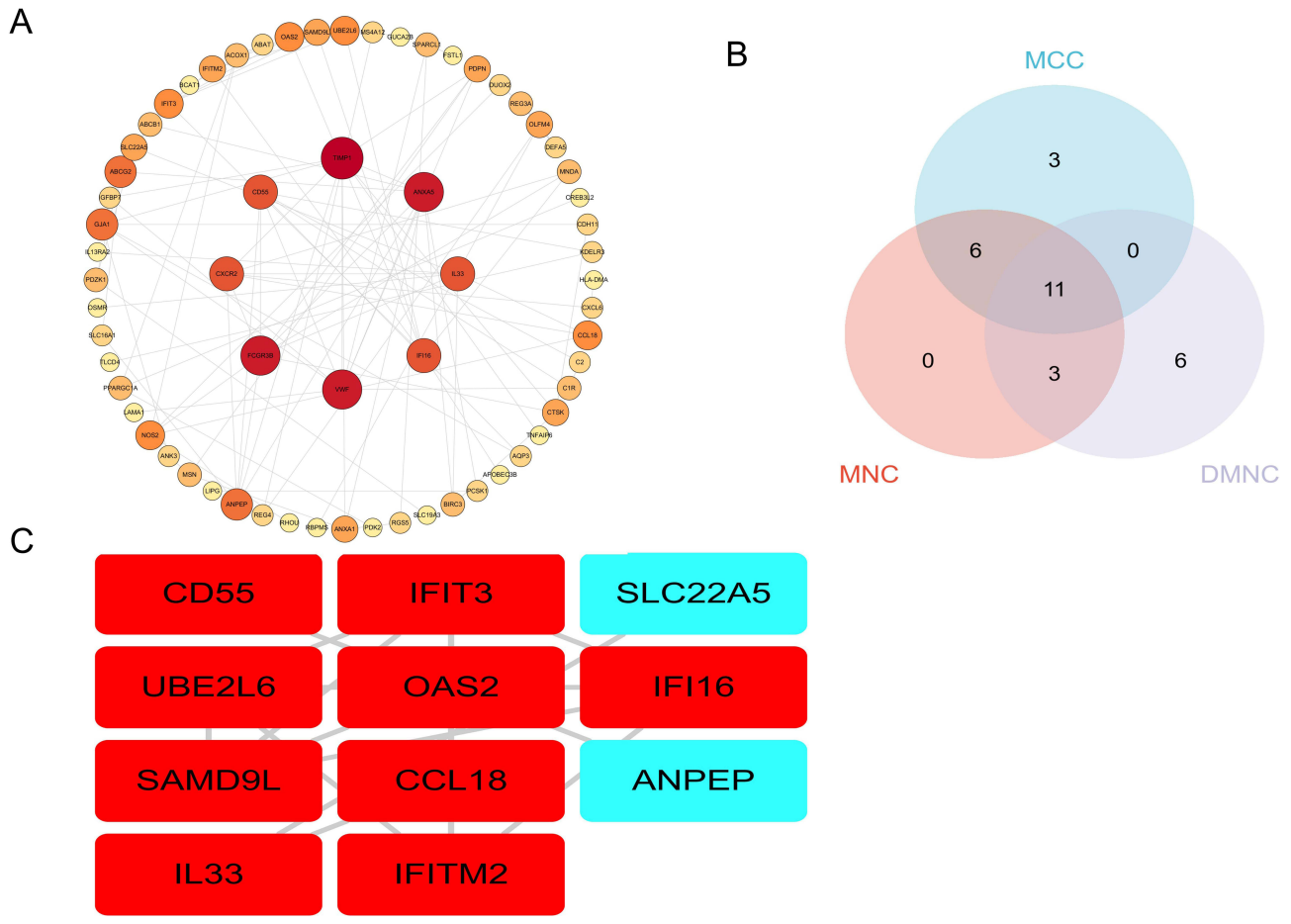

Figure 4 Screening of Hub genes. (**A**) Protein-protein interaction (PPI) network of common differential genes, where darker colors indicate a greater number of connections, and larger node sizes reflect higher connectivity. (**B**) Venn diagram illustrating the overlap of key genes identified by three algorithms. (**C**) Correlation maps of 11 key genes, with blue representing down-regulated genes and red indicating up-regulated genes.

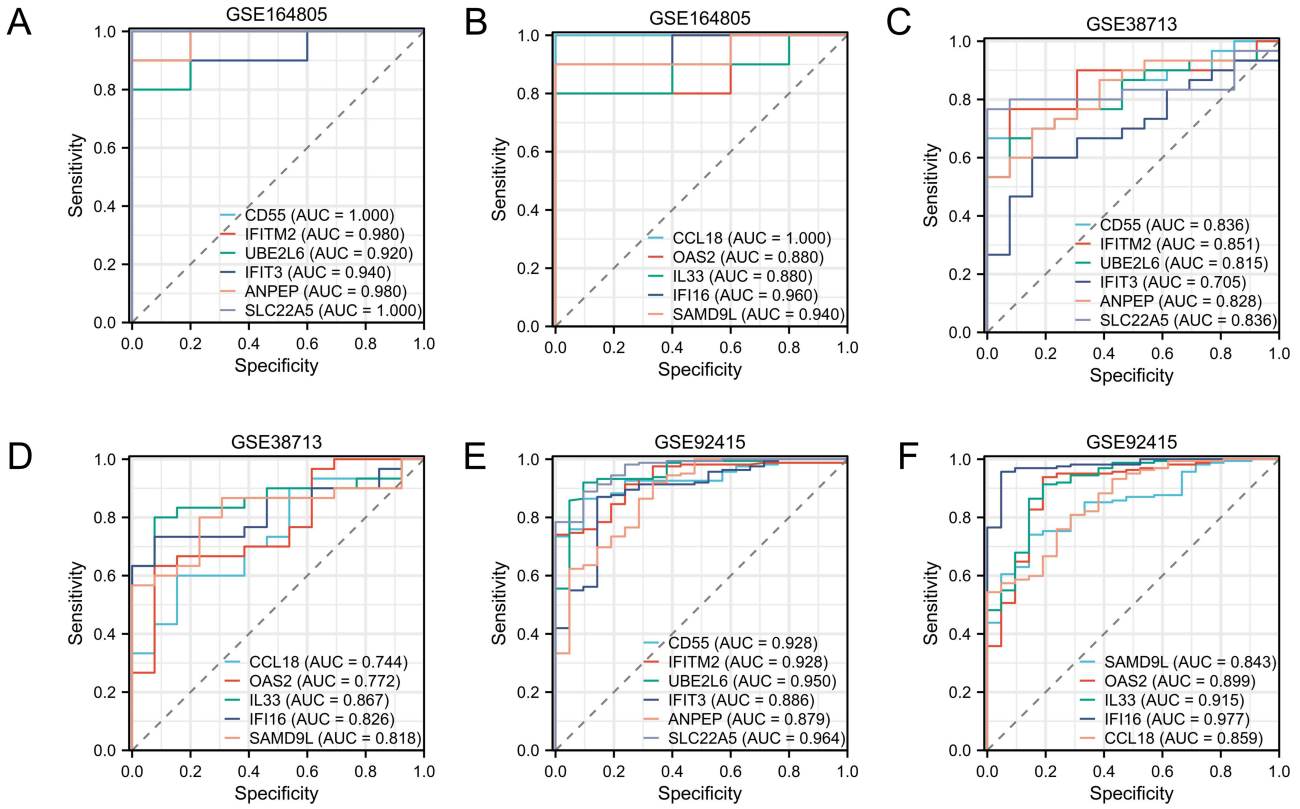

Figure 5 ROC analysis of key genes in the three datasets. (**A** and **B**) ROC analysis of key genes in dataset GSE164805; (**C** and **D**) ROC analysis of key genes in dataset GSE38713; (**E** and **F**) ROC analysis of key genes in dataset GSE192415.

(Figure 5). While these results indicate biomarker potential in a blood-based transcriptional context, further validation in independent cohorts and relevant tissues would be necessary to assess clinical diagnostic utility.

Construction of Regulatory Networks

To identify key molecules linking COVID-19 and primary sclerosing cholangitis (PSC), we employed a framework that incorporated gene-regulatory networks of transcription factors (TFs) and microRNAs (miRNAs) derived from differentially expressed genes (DEGs) and central genes. Utilizing the EnrichR database, we analyzed interaction networks of transcription factors, identifying 45 potential TFs that regulate common DEGs. We then constructed an interaction network involving the top 10 TFs, based on combined scores, and hub genes identified with these transcription factors (Figure 6), resulting in a network comprising 18 nodes and 14 edges.

Establishment of the miRNA-Gene Regulatory Network

Utilizing the miRTarBase module in EnrichR, we identified 1492 microRNAs (miRNAs) that potentially regulate common DEGs and constructed an interaction network between DEGs and the top 10 miRNAs (Figure 7), comprising 51 nodes and 64 edges.

Matching Potential Drugs

The DSigDB module from the EnrichR database was utilized to identify small-molecule drugs associated with common differentially expressed genes (DEGs), aiming to explore personalized treatment options for patients with COVID-19 and UC. Through comprehensive analysis, excluding ineffective factors, we confirmed the top 10 of 236 related drugs (Table 1). These findings suggest that these drugs have the potential to be used as therapeutics to treat. COVID-19 and UC.

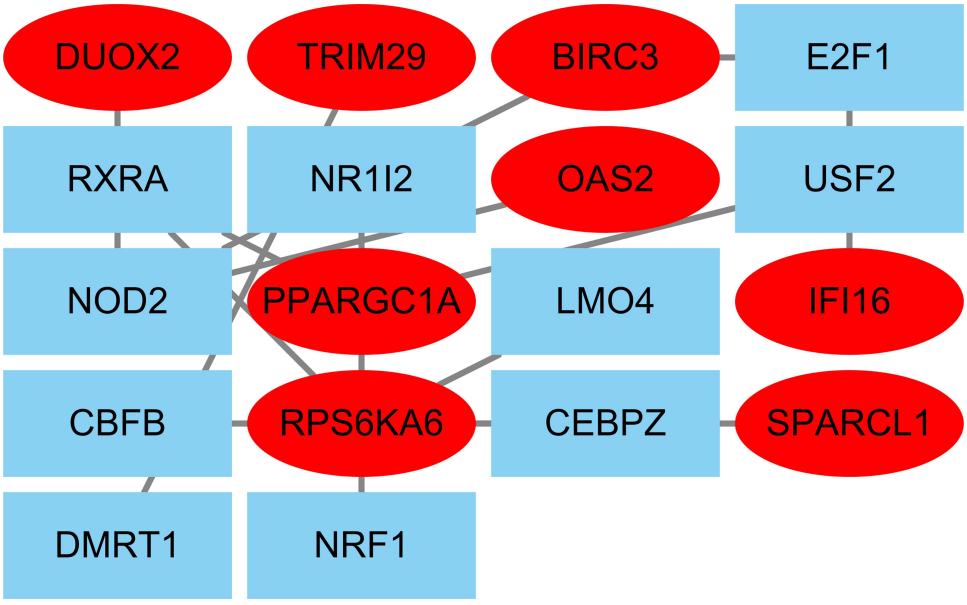

Figure 6 Transcription Factor-Gene Interaction Network. TFs are represented as red ovals, while DEGs are represented as blue rectangles.

Identification of Disease Relevance

In-depth network analysis has elucidated the complex relationships between genes and diseases, offering new insights into the development of treatment strategies. Significant associations were identified between our core genes and various diseases, including metastasis, tumor progression, cirrhosis, colon cancer, adenocarcinoma, psoriasis, endometriosis, and vascular neoplasms (Figure 8).

Discussion

The incidence of ulcerative colitis (UC) in patients infected with COVID-19 has been shown to be significantly increased,[21] and the prognosis for these individuals is notably poor. COVID-19, as a global pandemic, has been shown to cause pathological changes in multiple organs, including the digestive system. Research has indicated that the gastrointestinal tract can serve as both a reservoir and a route of transmission for the virus, leading to symptoms such as diarrhea, abdominal pain, and other gastrointestinal disturbances. A number of relevant studies have revealed the inflammatory and immune response mechanisms that may be involved in the process of COVID-19 infection.[22] These mechanisms often overlap with the pathophysiological features of UC, which is characterized by chronic inflammation of the colonic mucosa. With this in mind, we delve into possible common biological functions and pathways between COVID-19 and ulcerative colitis, aiming to uncover the interrelationship between the two diseases. This exploration is critical not only for understanding the shared pathways that contribute to disease exacerbation in patients suffering from both conditions but also for identifying potential therapeutic targets that could be leveraged for improved management and treatment strategies.

We acknowledge that a limitation of this study is the reliance solely on retrospective bioinformatic analysis of public genomic datasets (GSE164805, GSE38713, GSE92415) without experimental or prospective clinical validation; therefore, the diagnostic performance and clinical applicability of these biomarkers require further verification in independent cohorts and functional studies.

Research Advances of IFI16, IL-33, and CD55 as Potential Therapeutic Targets

In this study, we identified 115 differentially expressed genes (DEGs) and conducted a detailed functional annotation analysis of these genes. The Gene Ontology (GO) analysis revealed that these DEGs are primarily enriched in key biological processes, including inflammatory response, cell proliferation and differentiation, and immune regulation,

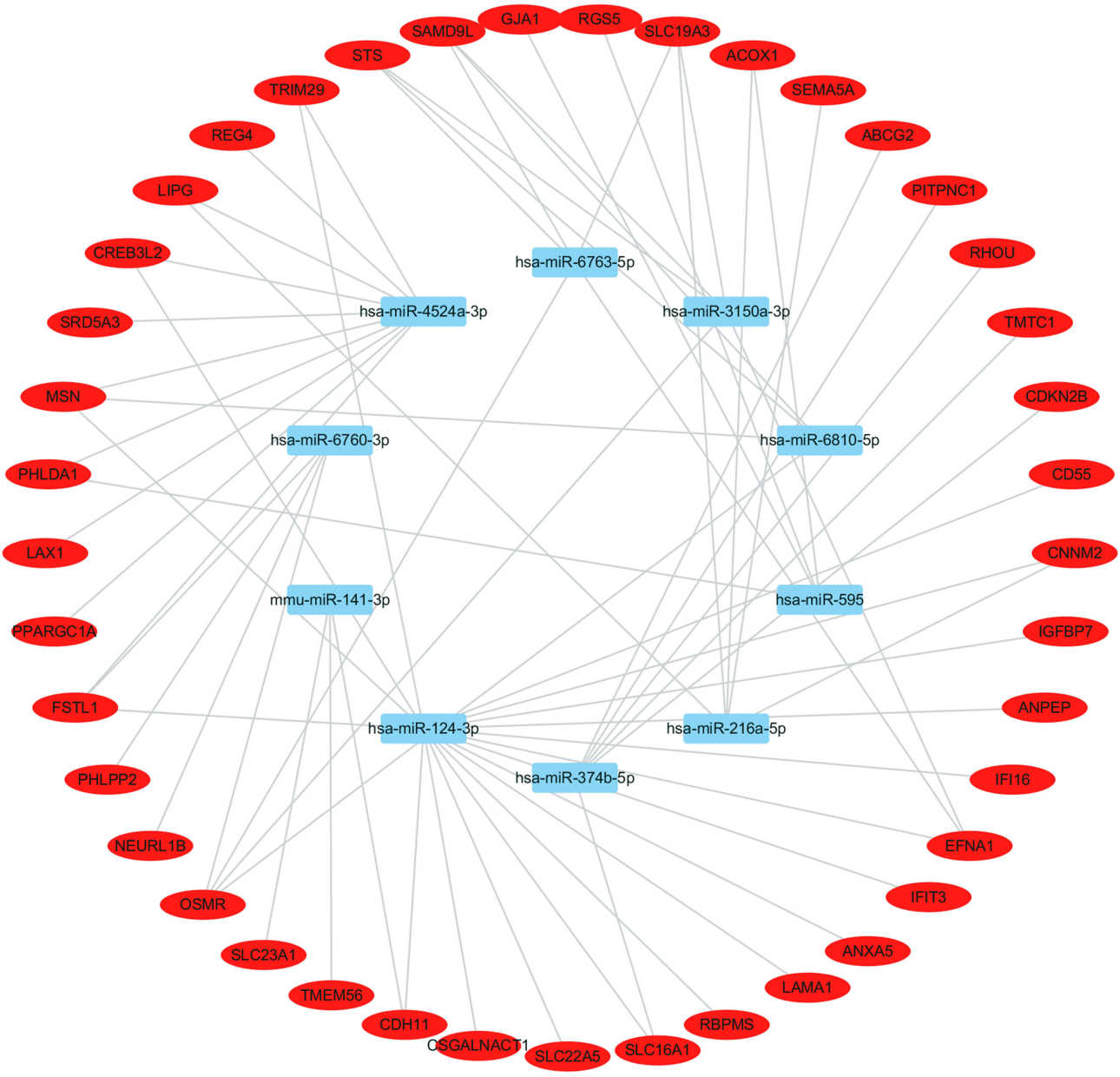

Figure 7 miRNA-Gene Interaction Network Diagram. MicroRNAs (miRNAs) are represented as blue rectangles, while differentially expressed genes (DEGs) are depicted as red ovals.

which align closely with the known pathological features of ulcerative colitis (UC) and COVID-19, thus validating our findings. The Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis indicated significant involvement of these genes in various signaling pathways related to disease occurrence and progression, particularly inflammation and apoptosis pathways. Dysregulation of these pathways may contribute to the pathogenesis of both UC and COVID-19.

Through comprehensive protein-protein interaction (PPI) network analysis, we identified 11 pivotal genes: IFI16, UBE2L6, OAS2, IFIT3, SAMD9L, IFITM2, ANPEP, IL33, CD55, CCL18, and SLC22A5. Notably, IFI16, IL33, and CD55 may play critical roles in the onset of COVID-19 pneumonia and ulcerative colitis.

IFI16 is crucial in both COVID-19 and ulcerative colitis (UC). In COVID-19, IFI16 serves as a key immune regulatory molecule and may act as a potential biomarker for disease monitoring and management;[23] In UC, it participates in the DNA sensor pathway, driving inflammatory cell death and closely correlating with type I interferon activity, thereby promoting disease progression[24] The role of IL-33 in COVID-19 is also significant. As a key immune

https://doi.org/10.2147/JMDH.S543183

Table 1 Targeted Drugs Based on Central Gene Predictions

Drug Name	Overlap Ratio	*P* Value	Adjusted P-value	Odds Ratio
Cyclosporine	67/4825	4.99E-15	8.86E-12	4.437740822
Progesterone	41/1915	2.46E-14	2.18E-11	490.1803279
Estradiol	61/4336	1.59E-13	9.41E-11	4.124799653
Aflatoxin	46/3081	1.51E-10	6.69E-08	3.701263042
Retinoic acid	52/4258	7.83E-09	2.78E-06	3.076889402
Vitamin C	12/261	3.55E-08	1.05E-05	9.187507311
Tetrodotoxin	44/3768	8.65E-07	1.92E-04	2.689384427
Sulpidil	8/141	1.57E-06	3.08E-04	11.10364697
Genistein	22/1231	1.74E-06	3.08E-04	3.654241931
Tamoxifen	17/802	3.32E-06	5.04E-04	4.220720135

system regulator, IL-33 activates immune cells and exacerbates inflammatory responses during infection. In particular, elevated IL-33 levels during coronavirus-induced inflammatory storms can lead to over-activation and interaction of immune cells, resulting in severe lung injuries and systemic inflammatory reactions, thus worsening clinical outcomes[25,26] In UC, IL-33 acts as an inflammatory factor that significantly promotes disease pathogenesis[27] Additionally, CD55 has a distinct role in both conditions. In COVID-19 lung tissues, the overactivation of the complement system is associated with increased CD55 expression, which may represent a self-protective mechanism against infection;[28] In active UC, inflammatory stimuli enhance CD55 (DAF) expression and release, which may mitigate inflammatory damage but could also contribute to disease deterioration,[29,30] While these changes may reflect the body's self-protective responses, they may also inadvertently exacerbate disease progression.

The identification of these genes enhances our understanding of the pathogenesis of COVID-19 and ulcerative colitis while offering potential targets for future therapeutic strategies. By investigating the functions and regulatory mechanisms of these genes, we can develop more accurate and effective treatments, ultimately improving patient outcomes.

Hsa-miR-124-3p and NRF1: Pioneering New Directions in Disease Treatment

In our comprehensive analysis, we identified Hsa-miR-124-3p as a critical factor in the pathogenesis of ulcerative colitis (UC). This microRNA is intricately involved in modulating inflammatory processes, and its activity is notably inhibited by the overexpression of RAB27A, which exacerbates the inflammatory response in UC patients.[31] Elevated levels of RAB27A not only disrupt the normal regulatory mechanisms of hsa-miR-124-3p but also contribute to a pro-inflammatory environment that sustains the disease. Notably, the novel drug ABX464 has been shown to effectively suppress this inflammatory response by enhancing the expression of hsa-miR-124-3p, presenting a promising new approach for the treatment of ulcerative colitis,[32] By restoring the functional levels of hsa-miR-124-3p, ABX464 may help rebalance the inflammatory milieu and improve clinical outcomes. Thus, hsa-miR-124-3p has the potential to emerge as a valuable therapeutic target for UC, paving the way for innovative treatment strategies that harness microRNA modulation to mitigate inflammation and promote mucosal healing.

On the other hand, among the top 10 predicted transcription factors, NRF1 demonstrates significant relevance in the medical field. NRF1 is essential for maintaining mitochondrial homeostasis and cellular energy metabolism, which are crucial for the proper functioning of immune cells. In the context of COVID-19 infection, NRF1 plays an active role in regulating the mitochondrial function of CD8 T cells, potentially influencing the disease progression and immune response to the virus. The critical role of NRF1 in COVID-19-associated T cell dysfunction provides novel mechanistic insights and potential therapeutic targets for severe COVID-19.[33] This regulatory function is vital, as mitochondrial health directly impacts the ability of T cells to proliferate and mount an effective response against infections. Furthermore, in ulcerative colitis, NRF1 serves as a key predictor of treatment response, offering valuable insights for the development of personalized treatment regimens.[34] By evaluating NRF1 levels, clinicians could tailor therapies to enhance mitochondrial function and optimize immune responses in UC patients. This discovery not only enhances our understanding of the disease's pathogenesis but also establishes a strong foundation for future precision medicine

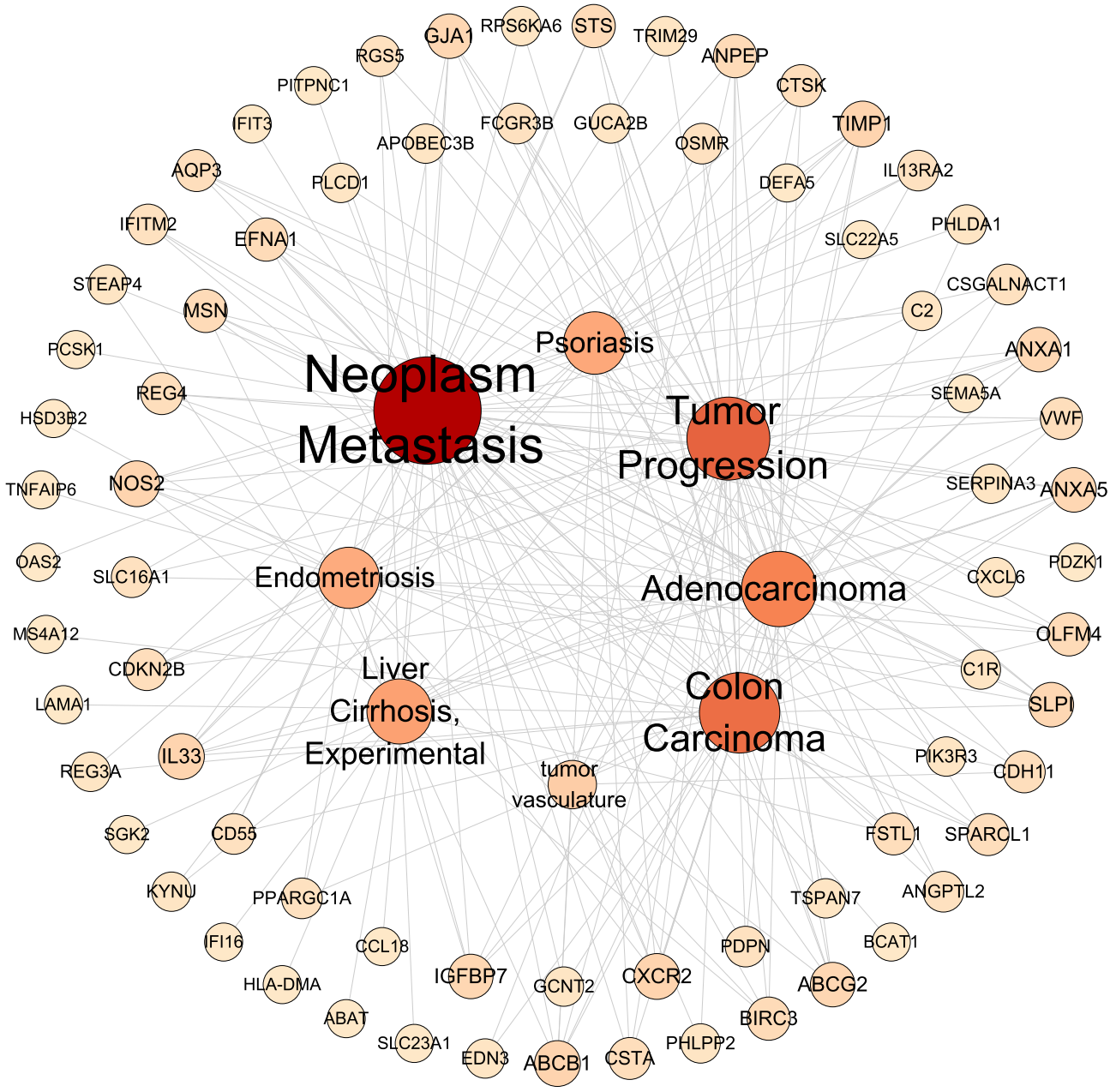

Figure 8 Disease-Gene Interaction Network. Related diseases are represented by hexagonal shapes, with darker colors indicating a greater number of connections, while differentially expressed genes (DEGs) are depicted as yellow oval shapes.

initiatives. By focusing on the roles of hsa-miR-124-3p and NRF1, we can advance our therapeutic strategies, providing a more comprehensive approach to managing ulcerative colitis and potentially improving outcomes in patients with coexisting conditions such as COVID-19.

New Treatment Strategies for COVID-19 and Ulcerative Colitis Using Cyclosporine and Retinoic Acid

Currently, there are no specific medications that have been validated for the simultaneous treatment of COVID-19 and ulcerative colitis (UC). Our study employs bioinformatics tools to identify small molecule drugs by analyzing common differentially expressed genes (DEGs) associated with both conditions. Among the candidate drugs, cyclosporine stands out for its demonstrated efficacy in alleviating acute severe UC by modulating the activity of neutrophils and inhibiting

inflammatory pathways.[35] This dual action underscores the potential for cyclosporine as a pivotal component in a combined treatment strategy.[36] In addition to cyclosporine, retinoic acid has emerged as a key player in regulating immune responses relevant to both diseases. Its deficiency has been implicated in immune dysregulation, which can exacerbate the clinical course of COVID-19, particularly through mechanisms like cytokine storms that result from excessive immune activation.[37] Retinoic acid not only aids in maintaining the integrity of the intestinal barrier, which is crucial for UC management, but also enhances the maturation and functionality of T cells. This is significant for antiviral immunity, suggesting that augmenting retinoic acid levels—potentially through dietary sources or supplementation—could provide additional support for both gut health and immune resilience in UC patients.[38] The selection of candidate drugs such as retinoic acid and cyclosporine was based on their high network centrality scores and support from existing mechanistic studies. Further experimental and clinical validation is warranted to confirm their efficacy and safety in the context of COVID-19 and ulcerative colitis.

Furthermore, corticosteroids such as 17β-estradiol (E2) and progesterone (P4) are known for their immunomodulatory and anti-inflammatory properties. Research has indicated that P4 may mitigate complications associated with COVID-19, such as acute respiratory distress syndrome (ARDS), by dampening the inflammatory response and stabilizing the immune system.[39] The ability of these corticosteroids to modulate inflammatory pathways makes them valuable candidates in the therapeutic arsenal against both UC and COVID-19. Their use could potentially minimize the risk of severe outcomes associated with hyperinflammation in COVID-19 while managing UC flare-ups effectively.[40] The influence of sex hormones such as E2 and P4 must be considered within the context of patient demographics—particularly in female-predominant cohorts, where hormonal status may shape both disease mechanisms and treatment outcomes. Future studies should incorporate sex-stratified analyses and account for gender-specific therapeutic responses to ensure clinically safe and personalized translation.

In terms of practical application, the combination of cyclosporine, retinoic acid, and corticosteroids could offer a multifaceted approach to treatment. This strategy would not only address the inflammatory processes inherent in both diseases but also potentially improve overall patient outcomes by reducing the severity and frequency of UC flare-ups and COVID-19 complications. Furthermore, ongoing clinical trials and studies exploring the safety and efficacy of these drugs in patients with comorbid conditions are crucial. Understanding the pharmacokinetics and interactions of these medications in diverse patient populations will be essential for developing guidelines that optimize therapeutic regimens.

Additionally, the role of gut microbiota in influencing both immune responses and treatment outcomes cannot be overlooked. Probiotics, particularly strains like Lactobacillus and Bifidobacterium, have been shown to enhance the immune response and may play a role in modulating inflammation in UC patients. Their potential to influence the gut-brain axis and systemic inflammation highlights the importance of a holistic approach to managing patients with dual diagnoses of UC and COVID-19. Prior to considering translational or clinical applications, the bioinformatic predictions require rigorous validation through well-designed in vitroand in vivoexperimental models.

In conclusion, our findings suggest that cyclosporine and retinoic acid (or their derivatives) may offer substantial therapeutic benefits for both COVID-19 and UC through their immunomodulatory and anti-inflammatory effects. While promising, further clinical trials and extensive research are necessary to validate the safety, efficacy, and optimal treatment protocols for these drugs in patients with overlapping conditions. We anticipate that continued investigation into these therapeutic agents will pave the way for more effective management of COVID-19 and UC, particularly in complex cases where their synergistic effects could significantly enhance patient outcomes.

New Insights into the Pathogenesis of UC and COVID-19 and Their Impact on Cross-Disease Treatment

This study has made significant strides in understanding the pathogenesis of ulcerative colitis (UC) and COVID-19, revealing an unexpected molecular link between these two seemingly unrelated diseases. Recent research indicates that the inflammatory pathways activated in UC may share similarities with those engaged during COVID-19, particularly concerning immune responses and cytokine signaling.[41] Through network analysis, we identified important associations between differentially expressed genes (DEGs) and a variety of other diseases, including cancer and cirrhosis, which

highlights the shared gene expression changes across diverse pathological states. These findings underscore the interconnectedness of diseases, providing valuable insights for future cross-disease research and the development of therapeutic strategies.

Moreover, understanding the functions of DEGs is crucial for identifying effective therapeutic targets. Gene function studies reveal that specific DEGs can modulate immune responses, making them potential candidates for therapeutic intervention in both UC and COVID-19 (3). This research not only advances our scientific knowledge but also illustrates the potential for repurposing existing drugs and discovering novel agents targeting common pathways across different diseases (4). Moving forward, it is essential to explore the relationships between various diseases at the molecular level using advanced technologies like multi-omics analyses. By fostering interdisciplinary collaboration, we can enhance our understanding of complex disease interactions and improve patient outcomes in the face of multifaceted health challenges.[42]

Bioinformatics Analysis of UC and COVID-19: Exploring Research Limitations and Potential

While this study provides insights into the shared molecular mechanisms between ulcerative colitis (UC) and COVID-19, several limitations must be acknowledged.

First, the reliance on publicly available transcriptomic datasets derived from peripheral blood—a highly heterogeneous tissue—introduces potential confounding due to variations in cellular composition across samples. Although computational methods were applied to mitigate this issue, the absence of cell-type-specific validation remains a constraint. Second, the modest sample sizes in certain cohorts (16 controls vs 31 COVID-19 cases; 30 controls vs 13 UC cases in one subset) limit the statistical power to detect modest expression changes and reduce the generalizability of the findings. Future studies should incorporate larger, well-matched cohorts with single-cell or cell-sorted transcriptomics to enhance resolution.

Furthermore, although functional enrichment analyses (GO, KEGG, PPI) offered mechanistic hypotheses, these databases are subject to curation bias, incomplete annotations, and limited disease-specificity. The therapeutic associations predicted herein require rigorous validation through in vitroand in vivomodels to establish biological and clinical relevance. Finally, the absence of comprehensive clinical metadata—such as detailed medication history, disease activity indices, and comorbidities—precluded adjustment for potential confounders that may influence gene expression patterns.

Despite these limitations, this study underscores the value of integrative bioinformatics in hypothesis generation. Future work should prioritize multi-omics integration, deeply phenotyped cohorts, and functional studies to translate these findings into targeted therapeutic strategies.

Conclusion

This study, based on transcriptional data, identified common differentially expressed genes (DEGs) associated with COVID-19 and ulcerative colitis (UC). The analysis revealed key signaling pathways, hub genes, and regulatory networks, suggesting that these two diseases share certain aspects of their pathogenesis. Additionally, small molecular compounds were screened to identify potential therapeutic targets for the treatment of COVID-19, particularly in patients with concurrent UC. These findings aim to contribute to the development of personalized treatment strategies for affected individuals.

Ethics Statement

This study utilized data obtained from public databases (eg, GEO, TCGA). All data were de-identified and contained no personal information. In accordance with Article 32, Items 1 and 2 of the "Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects" (issued by the National Health Commission of China, Ministry of Education, Ministry of Science and Technologyet al, February 18, 2023), ethical review is exempted for studies using publicly available anonymized data that cannot identify specific individuals and involve no personal privacy or

commercial interests. This study met the above criteria for exemption and therefore did not require additional ethical approval from an institutional review board.

Acknowledgments

The authors sincerely thank the GEO database for its platform and valuable dataset. We also appreciate the support and insightful discussions from colleagues at the Medical College of Yangzhou University, the Affiliated Hospital of Yangzhou University, Jinling Hospital affiliated with Nanjing University, and Nanjing Hospital of Traditional Chinese Medicine.

Funding

This research received funding from the National Natural Science Foundation of China (grant number 82273084). Medical Research Project approved by Health Commission of Jiangsu Province, ZD2022011.

Disclosure

The authors report no conflicts of interest in this work.

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