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Identification of shared hub genes in lung cancer and rheumatoid arthritis patients using bioinformatics approaches

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ABSTRACT

Objectives:To identify key genes common to lung cancer and rheumatoid arthritis through WGCNA co-expression network and MCC algorithm analysis.

Methods: Initially, chip data related to lung cancer and rheumatoid arthritis were obtained from the GEO database for data integration and differential analysis, leading to the identification of key differentially expressed genes. Subsequently, WGCNA was utilized to construct a co-expression network, identifying susceptible modules and core genes. Further, common core genes in lung cancer and rheumatoid arthritis were identified through Venn diagrams, assessing their diagnostic accuracy in disease, analyzing differential expression, and constructing a co-expression network. Finally, GO and KEGG enrichment analyses were conducted to understand the functions and pathway enrichment of these core genes, and potential target drugs were predicted.

Results: Six lung cancer-related and three rheumatoid arthritis-related gene co-expression modules were constructed using WGCNA. The Turquoise module was identified as the susceptible module for lung cancer, while the Blue module was for rheumatoid arthritis. A total of 953 genes were included in the lung cancer hub genes, and 152 in the rheumatoid arthritis hub genes. Finally, 92 potential target drugs were predicted through the DGIdb database that may regulate the expression of 11 common hub genes.

Conclusion: We identified 24 common hub genes for lung cancer and rheumatoid arthritis, with the top 6 ranked by the MCC algorithm being FGR, SLA, GZMH, CSF2RB, PRF1, and CCRL2. This study paves the way for further exploration of the common pathogenesis of lung cancer and rheumatoid arthritis. However, further in vivo and in vitro experiments are required for validation and support.

Keywords: WGCNA co-expression network, lung cancer, rheumatoid arthritis, key genes, bioinformatics

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INTRODUCTION

Lung cancer, recognized as a malignant neoplasm, stems from lung tissues and is marked by unregulated cellular growth and the capacity to infiltrate adjacent tissues. It is widely acknowledged that smoking is a primary risk factor for this disease, although it is also influenced by environmental factors, genetic variations, and occupational exposures [1]. Global epidemiological research indicates a rising trend in lung cancer prevalence, especially in non-small cell lung cancer, where rates have escalated from 175.3 to 198.3, as per the National SEER-18 estimates [2]. Rheumatoid arthritis (RA) is an enduring autoimmune condition distinguished by symptoms such as discomfort, swelling in the joints, diminished functionality, and the deterioration of bone structure. RA can also lead to systemic organ inflammation and damage, increasing the risk of complications such as cardiovascular and pulmonary diseases [3]. Risk factors for RA include genetic inheritance, gender, environmental factors, and immune system abnormalities [4].Worldwide, the occurrence rate of RA is estimated to be around 0.5% [5].

There are various connections between lung cancer and RA, including interactions of the immune system, common inflammatory pathways, and intersections of therapeutic interventions [6]. A meta-analytical study indicates a heightened risk of lung cancer (LC) due to radiation in patients with RA, with a relative risk (RR) of 1.44 and a 95% confidence interval (CI) ranging from 1.31 to 1.57 [7]. The risk of lung cancer in RA patients is estimated to be elevated by about 1.5 to 3.5 times. Furthermore, data support lung malignancies as the most common cause of cancer-related deaths in RA patients,

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particularly in male patients and those with interstitial lung disease (ILD) [8]. Therefore, a deeper understanding of the shared pathogenic mechanisms of these two diseases may offer valuable insights for improving patient diagnosis and treatment strategies.

Weighted Gene Co-expression Network Analysis (WGCNA) is a systematic biology tool used to describe patterns of gene expression related to sample characteristics. WGCNA investigates thousands of genes, identifies gene modules of clinical interest, and uses module connectivity to determine key genes that aid in understanding the molecular mechanisms of complex diseases [9]. A key benefit of WGCNA lies in its capacity to transform gene expression data into co-expression modules, effectively linking sample characteristics with alterations in gene expression. WGCNA provides a systemic insight that is highly sensitive to low-abundance or small-fold-change genes without any information loss and has been widely applied in various research fields, including disease, evolution, biomedicine, and clinical medicine [10]. Past research has demonstrated that WGCNA identifies vital modules and pathways across various diseases and pinpoints key characteristic genes.

Although the etiology and specific mechanisms of lung cancer and rheumatoid arthritis differ, there is a clear correlation between them. This research intends to utilize WGCNA alongside the Maximum Clique Centrality (MCC) algorithm for uncovering shared crucial genes and associated signaling pathways in both lung cancer and rheumatoid arthritis, offering fresh perspectives on the biological underpinnings of these diseases.

MATERIALS AND METHODS

Data Acquisition

Using "Lung Cancer" and "Rheumatoid Arthritis" as keywords, microarray data related to lung cancer and rheumatoid arthritis were retrieved from the Gene Expression Omnibus (GEO) database. We acquired lung cancer microarrays with accession numbers GSE18842 and GSE43458. The GSE18842 microarray includes samples from 45 healthy controls and 46 tumor patients, based on the GPL570 platform. These tumor samples were obtained from primary malignant lung tumors of untreated patients. The GSE43458 microarray comprises 30 non-smoking healthy controls and 40 non-smoking tumor patients, utilizing the GPL6244 platform. For rheumatoid arthritis, microarrays with accession numbers GSE1919, GSE55235, and GSE77298 were obtained. The GSE1919 microarray, on the GPL91 platform, includes samples from 5 healthy controls and 5 rheumatoid arthritis patients. The GSE55235 microarray consists of 10 healthy controls and 10 rheumatoid arthritis patients, using the GPL96 platform. Lastly, the GSE77298 microarray, based on the GPL570 platform, includes 7 healthy controls and 16 rheumatoid arthritis patients.

Differential Analysis

The acquired microarray datasets for lung cancer and rheumatoid arthritis were merged and batch-corrected. The "limma" package in R was used to analyze differential gene expression levels between lung cancer samples and healthy samples, as well as between rheumatoid arthritis samples and healthy samples. Heatmaps and volcano plots were generated for visualization. Parameters were set as log2FC = 0.585 and adj. P. Value≤0.05.

WGCNA Network Construction and Identification of Susceptibility Modules and Core Genes

The "WGCNA" package in R was employed to build the WGCNA co-expression network. Initially, clustering of samples was conducted to identify any prominent outliers. Subsequently, the soft-thresholding power β was determined, and co-expression similarity was evaluated for adjacency computation. For analyzing network topology, the "pickSoftThreshold" function within WGCNA was utilized. Third, gene clustering, dynamic module identification, and the clustering merge of similar modules were carried out. Fourth, an evaluation of the correlation between modules and clinical characteristics was carried out, followed by the calculation of module membership (MM) and gene significance (GS). The most important module was selected, and scatter plots of trait and module were generated. Hub genes were extracted from this module, with GS values exceeding 0.3 and MM values exceeding 0.6 included as Hub genes.

Screening and Analysis of Common HubGenes for Lung Cancer and Rheumatoid Arthritis

First, a Venn diagram was used to map the obtained Hub genes for lung cancer and rheumatoid arthritis, resulting in common Hub genes. ROC curves were employed to assess the accuracy of common Hub genes for diagnosing lung cancer and rheumatoid arthritis, respectively. Subsequently, the differential expression of each common Hub gene between lung cancer samples and healthy samples, as well as between rheumatoid arthritis samples and healthy samples, was analyzed. Ultimately, a co-expression network for these Hub genes was established utilizing the GeneMANIA database.

Gene Ontology (GO) Functional Enrichment Analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Enrichment Analysis

ID conversion of common Hub genes was performed in R. The "clusterProfiler" package in R was used to conduct GO and KEGG enrichment analyses of common Hub

genes under the conditions of p-value≤0.05 and q-value = 1, with the results visualized.

Construction of Protein-Protein Interaction (PPI) Network and Secondary Selection of Common HubGenes

The PPI network for common Hub genes was analyzed in the STRING database (species set as "Homo Sapiens") and visualized in Cytoscape 3.7.2. The top 6 common Hub genes were assessed and selected using the MCC algorithm in the cytoHubba plugin.

Prediction of Targeted Drugs for Common HubGenes

To pinpoint drugs targeting common Hub genes and to delineate their interconnections, the Drug-Gene Interaction database (DGIdb) (available at https://dgidb.genome.wustl.edu/) was employed, facilitating the construction of a drug-gene regulatory network.

RESULTS

Analysis of Differential Genes in Lung Cancer and Rheumatoid Arthritis

Perl and R language tools were utilized to merge and batch-correct the acquired lung cancer and rheumatoid arthritis-related microarray data. Subsequently, differential analysis was performed using the "limma" package in R. The results revealed that compared to the healthy control group, lung cancer patients exhibited 2609 differentially expressed genes (Figure 1A). In contrast, rheumatoid arthritis patients showed 385 differentially expressed genes compared to the healthy control group (Figure 1B). Volcano plots were used to visualize these results. The top 50 most significantly upregulated and downregulated genes were selected to construct clustering heatmaps (Figures 1C-D).

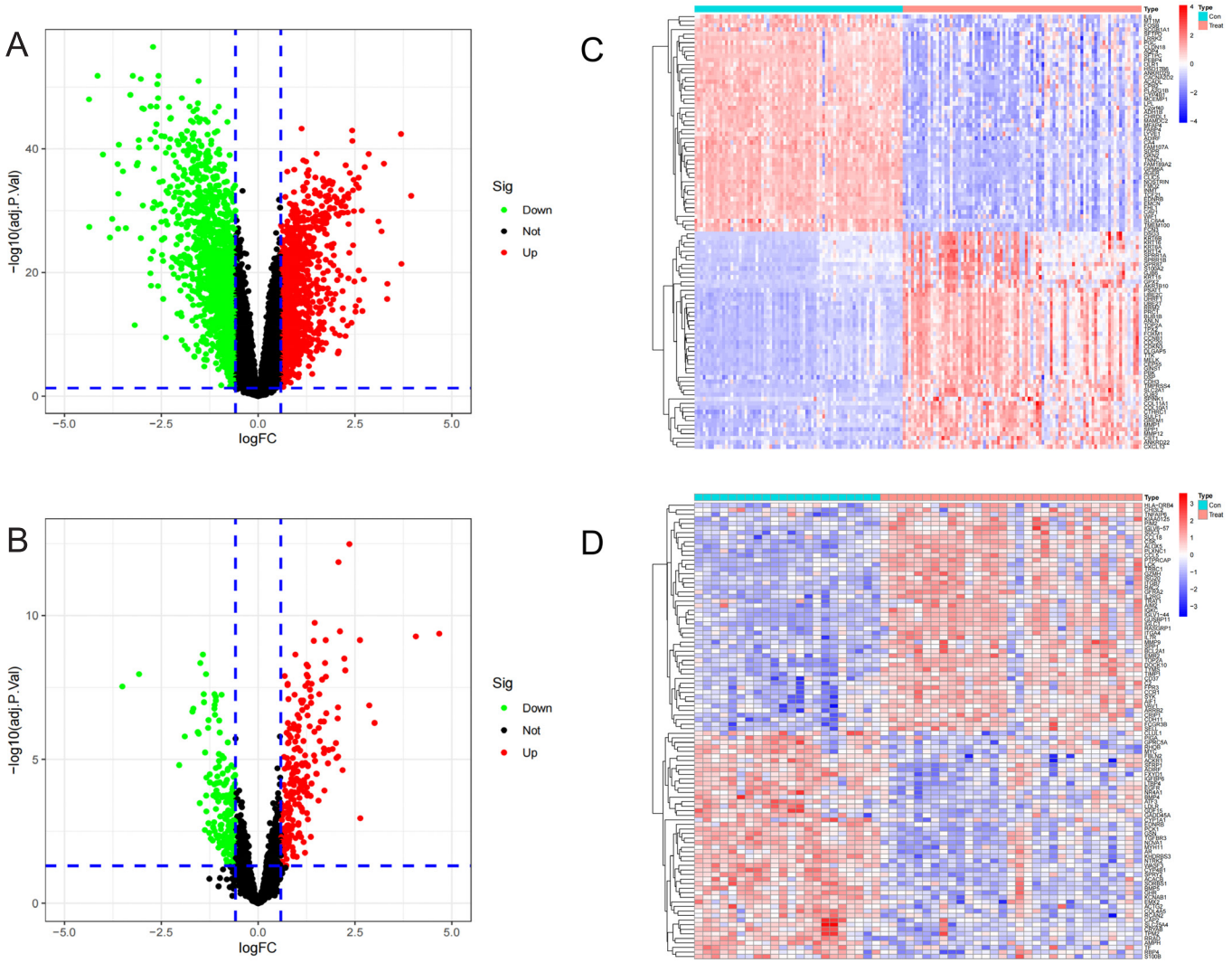


Fig. 1. Volcano Plots and Clustered Heatmaps (A) Volcano Plot for Lung Cancer (B) Volcano Plot for Rheumatoid Arthritis (C) Clustered Heatmap for Lung Cancer (D) Clustered Heatmap for Rheumatoid Arthritis.

Construction of WGCNA Co-expression Networks

To construct the WGCNA network, we first conducted clustering of the samples, which revealed no apparent outliers. The soft threshold power β was computed to suggest a uniform expression similarity for adjacency determination. We used the pickSoftThreshold function within WGCNA for network topology analysis. In analyzing lung cancer, we set the soft threshold power β to 9, attaining a scale-free fit index of 0.9 (Figure 2A). For the rheumatoid arthritis analysis, the β value was established at 3, reaching a scale-free fit index of 0.9 (Figure 2B). Both exhibited relatively high mean connectivity, indicating that the WGCNA networks for lung cancer and rheumatoid arthritis conform to a power-law distribution, closely resembling real biological network states. Finally, we used the WGCNA R package for gene clustering and dynamic tree cutting for module identification. This process constructed a gene dendrogram and identified module colors (Figure 2C). Similar modules were clustered and merged, leading to the construction of a gene dendrogram and identification of merged module colors (Figure 2D). Ultimately, six lung cancer-related and three rheumatoid arthritis-related gene co-expression modules were constructed.

Determination of Susceptibility Modules and Hub Genes

We conducted an analysis of the correlation between modules and clinical traits. In the lung cancer analysis, the blue, brown, green, turquoise, yellow, and grey modules all had P-values less than 0.05, indicating significant correlations (Figure 3A). In the rheumatoid arthritis analysis, the blue, brown, and turquoise modules also had P-values less than 0.05, indicating significant correlations (Figure 3B). Module membership (MM) values and gene significance (GS) values were calculated to analyze the importance of gene expression levels in each module for lung cancer and rheumatoid arthritis. The results indicated that the most significant module for lung cancer was the turquoise module (Figure 3C), and for rheumatoid arthritis, it was the blue module (Figure 3D). Therefore, the turquoise module was identified as the susceptible module for lung cancer due to its significant correlation, and the blue module was identified as the susceptible module for rheumatoid arthritis. A scatter plot of the genes in the turquoise module, which includes 1767 genes, was created (Figure 3E). Similarly, a scatter plot for the blue module, containing 475 genes, was generated (Figure 3F). Finally, using a filtering criterion of GS values over 0.3 and MM values over 0.6, 953 genes were included as hub genes for lung cancer, and 152 genes as hub genes for rheumatoid arthritis.

Selection and Analysis of Common Hub Genes for Lung Cancer and Rheumatoid Arthritis

Using R language, we mapped and intersected 953 hub genes from lung cancer with 152 hub genes from rheumatoid arthritis, identifying 25 common hub genes for both diseases (Figure 4A). ROC curves were utilized to determine the accuracy of these 25 common hub genes in diagnosing lung cancer and rheumatoid arthritis. The area under the curve (AUC) is indicative of the predictive accuracy of the genes; a higher AUC value signifies greater accuracy. The results showed that all 25 common hub genes had high predictive accuracy in lung cancer samples (Figure 4B), but only 24 of them showed high predictive accuracy in rheumatoid arthritis samples (Figure 4C). Consequently, we identified 24 common hub genes as characteristic genes for diagnosing both diseases: ADIRF, ALOX5, BMP5, CCRL2, CRYAB, CSF2RB, CYP4B1, DOK2, FGR, FHL1, GDF10, GZMH, H1F0, HCK, IL7R, KLRD1, PRF1, RBP4, SLA, SLC7A7, SPP1, TYMS, UBE2C, and WASF3. The differential expression levels of these 24 common characteristic genes among clinical traits in lung cancer samples are shown in Figure 5. H1F0, SPP1, TYMS, UBE2C were upregulated, while ADIRF, ALOX5, BMP5, CCRL2, CRYAB, CSF2RB, CYP4B1, DOK2, FGR, FHL1, GDF10, GZMH, HCK, IL7R, KLRD1, PRF1, RBP4, SLA, SLC7A7, WASF3 were downregulated in lung cancer samples. The differential expression levels among clinical traits in rheumatoid arthritis samples are depicted in Figure 6. CCRL2, CSF2RB, DOK2, FGR, GZMH, HCK, IL7R, KLRD1, PRF1, SLA, SPP1, TYMS, UBE2C, ALOX5, SLC7A7 were upregulated, while ADIRF, BMP5, CRYAB, CYP4B1, FHL1, GDF10, H1F0, RBP4, WASF3 were downregulated in rheumatoid arthritis samples. Table 1 presents the relevant information of these 24 common characteristic genes. Utilizing the GeneMANIA database, we analyzed the co-expression network and related functions of these 24 common characteristic genes. These genes exhibited a complex protein-protein interaction (PPI) network, with Co-expression at 83.82%, Physical Interactions at 8.74%, Shared Protein Domains at 3.75%, Co-localization at 3.19%, and Genetic Interactions at 0.51% (Figure 7).

Functional and KEGG Pathway Enrichment Analysis

Using the "clusterProfiler" package in R, we performed GO and KEGG enrichment analyses on the 24 common characteristic genes. The results were sorted based on p-values, and the top 10 most significantly enriched GO terms were presented. The GO enrichment analysis indicated major involvement in processes such as T cell-mediated cytotoxicity, negative regulation of immune response, negative regulation of T cell-mediated cyto-

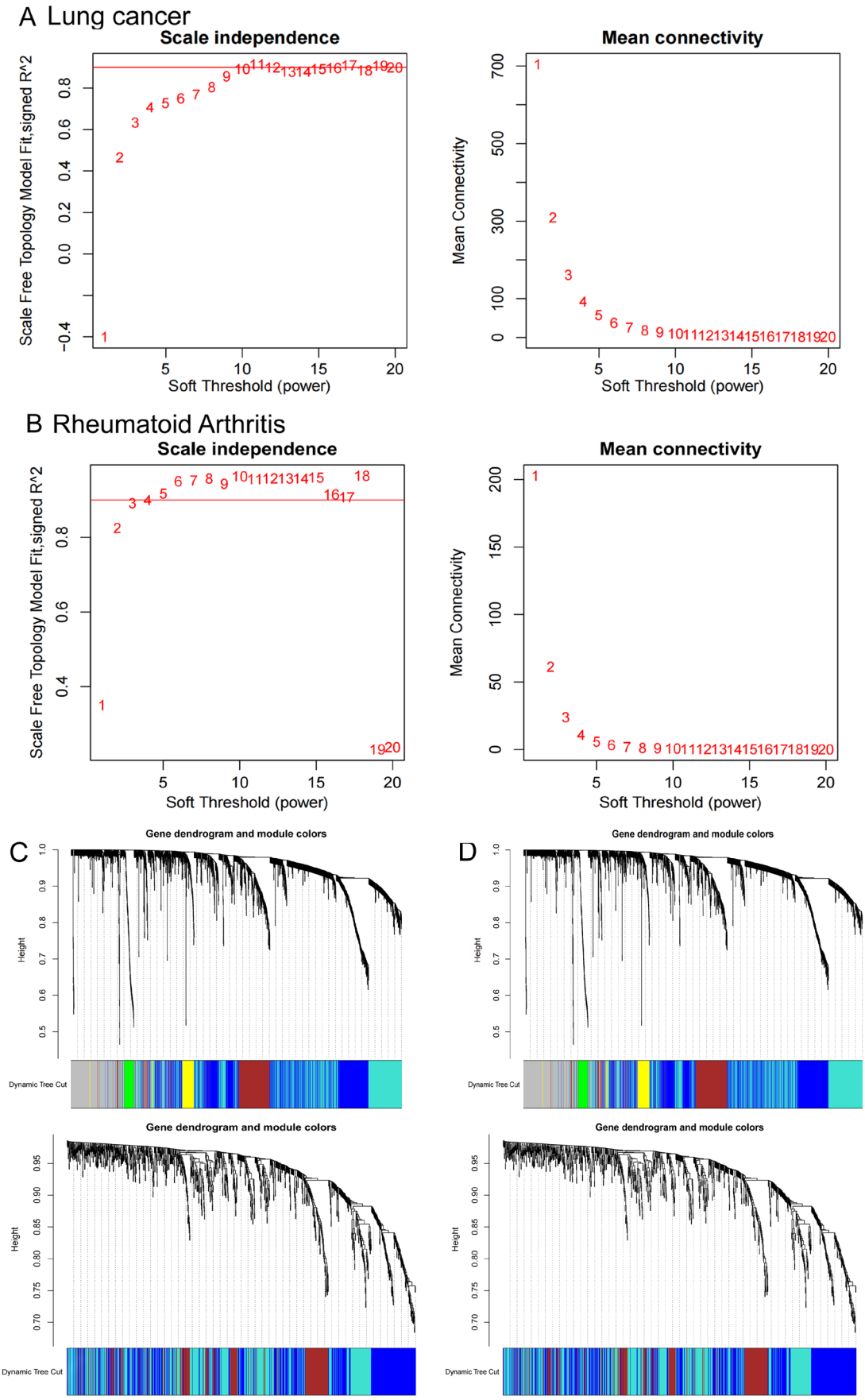
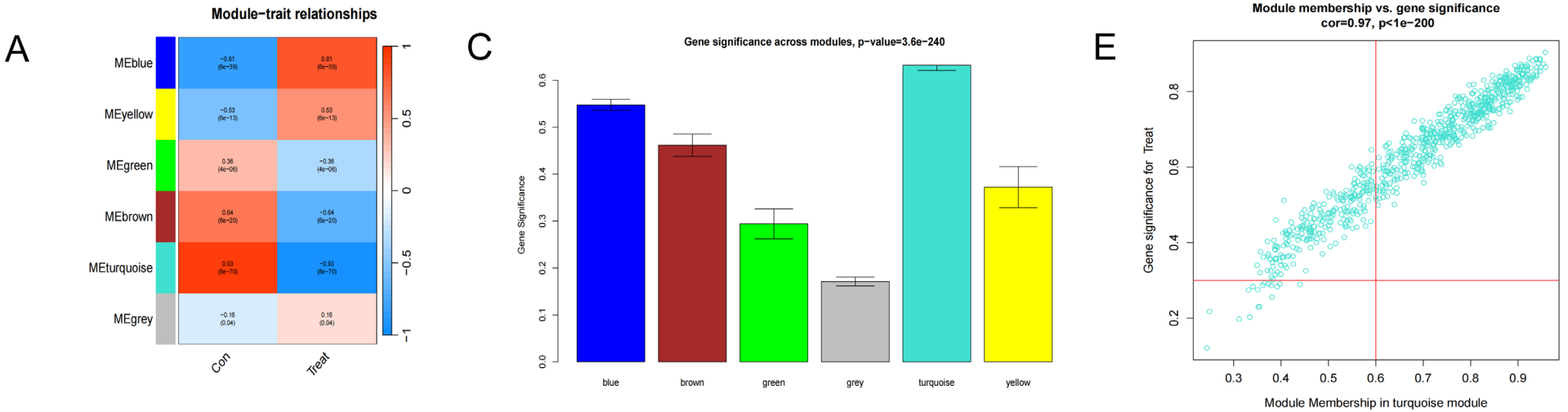


Fig. 2. Construction of WGCNA Co-expression Networks (A-B) Network Topology Analysis for Various Soft-Thresholding Powers (x-axis reflects the soft-threshold power, y-axis represents the scale-free topology model fit index and mean connectivity, respectively) (C) Dendrogram of Gene Clustering with Designated Module Colors (D) Dendrogram of Gene Clustering with Designated Colors for Merged Modules.

Lung cancer



Rheumatoid Arthritis

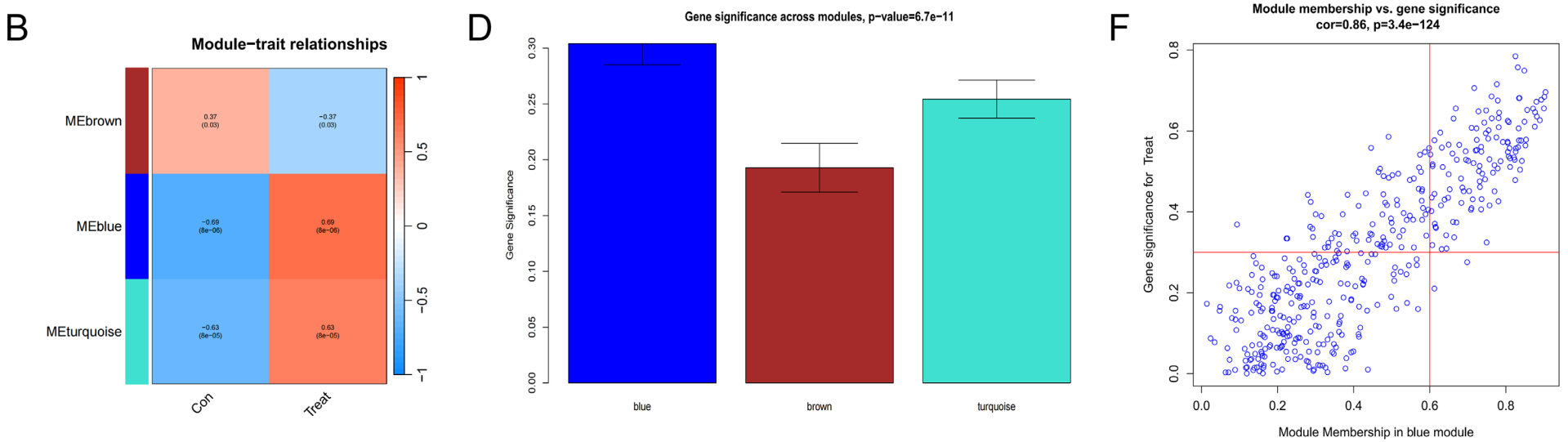


Fig. 3. Identification of Susceptible Modules and Core Genes (A) Module-Trait Relationships in Lung Cancer (B) Module-Trait Relationships in Rheumatoid Arthritis (C) Gene Significance in Various Modules for Lung Cancer (D) Gene Significance in Various Modules for Rheumatoid Arthritis (E) Scatter Plot of Genes in the Turquoise Module (F) Scatter Plot of Genes in the Blue Module.

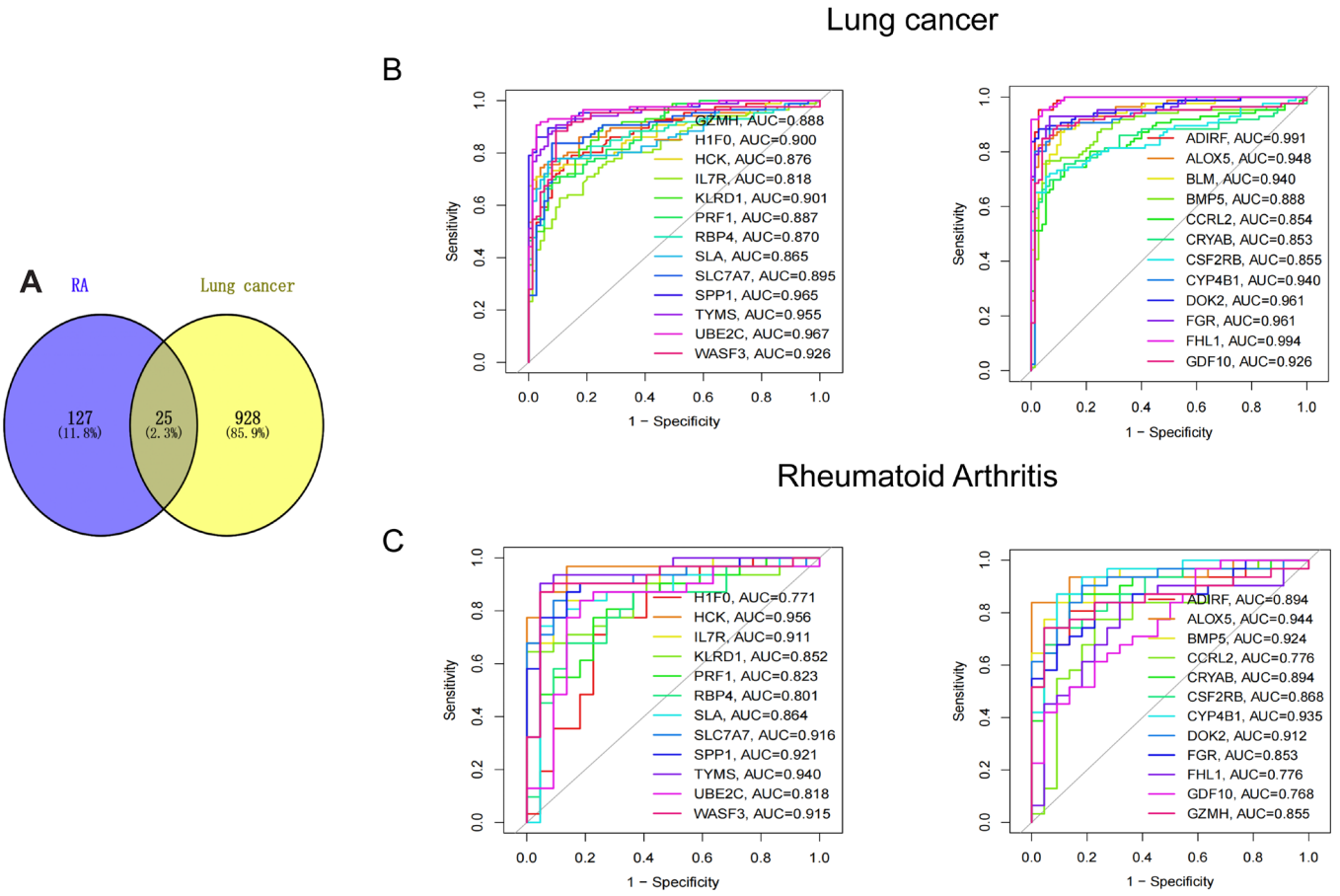


Fig. 4. Screening of Common Hub Genes (A) Venn Diagram of Common Hub Genes in Lung Cancer and Rheumatoid Arthritis (B) ROC Curve for 25 Common Hub Genes in Lung Cancer Samples (C) ROC Curve for 24 Common Hub Genes in Rheumatoid Arthritis Samples

toxicity, ossification, negative regulation of immune system process, negative regulation of response to external stimulus, leukocyte-mediated immunity, and negative regulation of growth (Figure 8A). The KEGG enrichment analysis revealed significant involvement in graft-versus-host disease, Fc gamma R-mediated phagocytosis, natural killer cell-mediated cytotoxicity, and one carbon pool (Figure 8B).

Construction and Analysis of Protein-Protein Interaction (PPI) Network

A PPI network with a confidence level greater than 0.15 was constructed using Cytoscape, comprising 22 nodes and 78 edges (Figure 9A). Utilizing the MCC algorithm of the cytoHubba plugin, we identified the top 6 common hub genes (Figure 9B), which included FGR, SLA, GZMH, CSF2RB, PRF1, and CCRL2. These proteins play a key role in the entire network and may be crucial genes in the pathogenesis and progression of lung cancer and rheumatoid arthritis.

Identification of Targeted Drugs for Common HubGenes

In this study, 92 potential target drugs were predicted through the DGIdb database to potentially regulate the expression of 11 common hub genes (ALOX5, BMP5, CSF2RB, CYP4B1, FGR, HCK, KLRD1, PRF1, RBP4, SPP1, TYMS). A drug-gene regulatory network was constructed (Figure 10) (Table 2). The results indicate that Methotrexate and Thalidomide are commonly used clinical drugs for the treatment of lung cancer and rheumatoid arthritis. However, the specific treatment regimen and drug selection should be determined by medical professionals based on the patient's individual circumstances. These drugs play a key role in the treatment of both diseases and require close monitoring to optimize therapeutic effects.

DISCUSSION

Microarray and high-throughput sequencing technologies are pivotal in exploring gene expression levels, facilitating a more profound understanding of the molecular mechanisms of complex diseases [11]. Identifying key differentially regulated genes and their target pathways is vital in elucidating the pathogenesis and progression of lung cancer and rheumatoid arthritis.

In this study, using WGCNA co-expression network analysis, we identified 24 common hub genes that serve

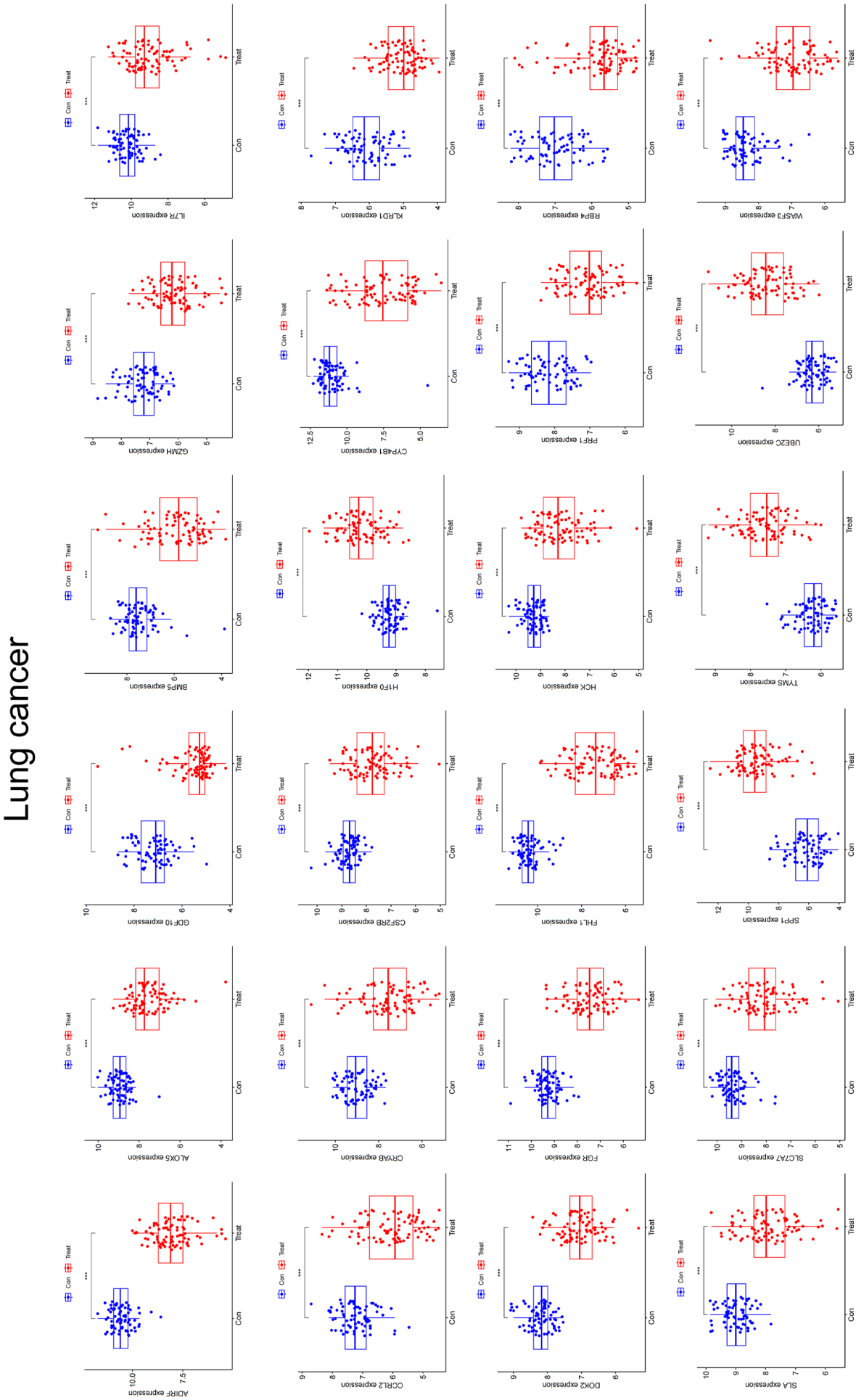


Fig. 5. Box Plot of Differential Expression Levels of 24 Common Feature Genes in Lung Cancer Samples (*p<0.05, **p<0.01, and ***p<0.001)

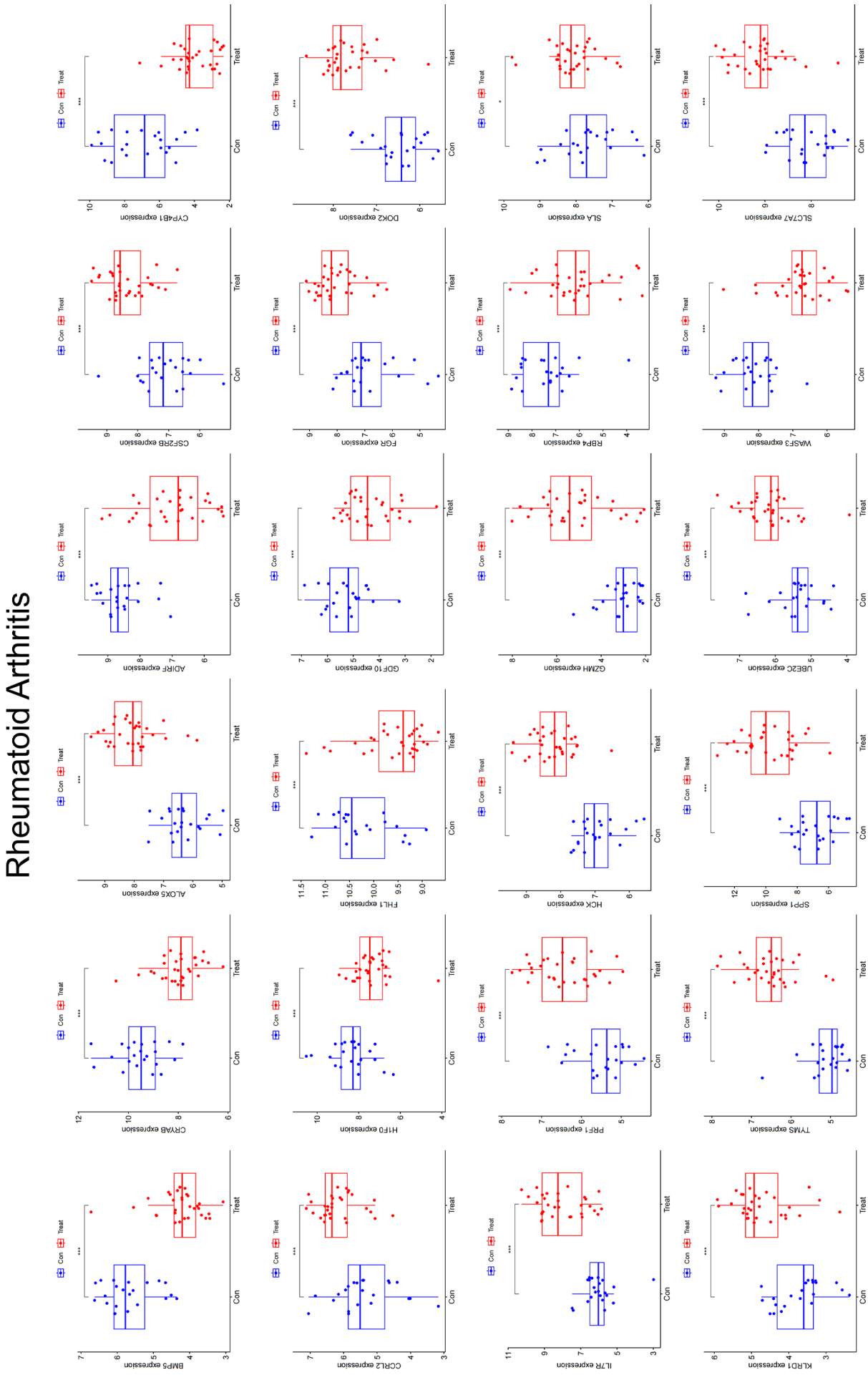


Fig. 6. Box Plot of Differential Expression Levels of 24 Common Feature Genes in Rheumatoid Arthritis Samples (*p<0.05, **p<0.01, and ***p<0.001)

Table 1. Detailed Information on the 24 Common Characteristic Genes

Gene	Description	Trend direction (Lung cancer)	Trend direction (Rheumatoid Arthritis)
CCRL2	Chemokine (C-C Motif) Receptor-Like 2	down	up
CSF2RB	Colony Stimulating Factor 2 Receptor Beta Common Subunit	down	up
DOK2	Docking Protein 2	down	up
FGR	Feline Gardner-Rasheed Sarcoma Viral Oncogene Homolog	down	up
GZMH	Granzyme H (Cathepsin G-Like 2, Protein H-CCPX)	down	up
HCK	Hemopoietic Cell Kinase	down	up
IL7R	Interleukin 7 Receptor	down	up
KLRD1	Killer Cell Lectin Like Receptor D1	down	up
PRF1	Perforin 1 (Pore Forming Protein)	down	up
SLA	Src-Like-Adaptor	down	up
SPP1	Secreted Phosphoprotein 1	up	up
TYMS	Thymidylate Synthetase	up	up
UBE2C	Ubiquitin Conjugating Enzyme E2 C	up	up
ALOX5	Arachidonate 5-Lipoxygenase	down	up
SLC7A7	Solute Carrier Family 7 (Amino Acid Transporter Light Chain, Y+L System), Member 7	down	up
ADIRF	Adipogenesis Regulatory Factor	down	down
BMP5	Bone Morphogenetic Protein 5	down	down
CRYAB	Crystallin Alpha B	down	down
CYP4B1	Cytochrome P450, Family 4, Subfamily B, Polypeptide 1	down	down
FHL1	Four And A Half LIM Domains 1	down	down
GDF10	Growth Differentiation Factor 10	down	down
H1F0	H1 Histone Family, Member 0	up	down
RBP4	Retinol Binding Protein 4	down	down
WASF3	Wiskott-Aldrich Syndrome Protein Family Member 3	down	down

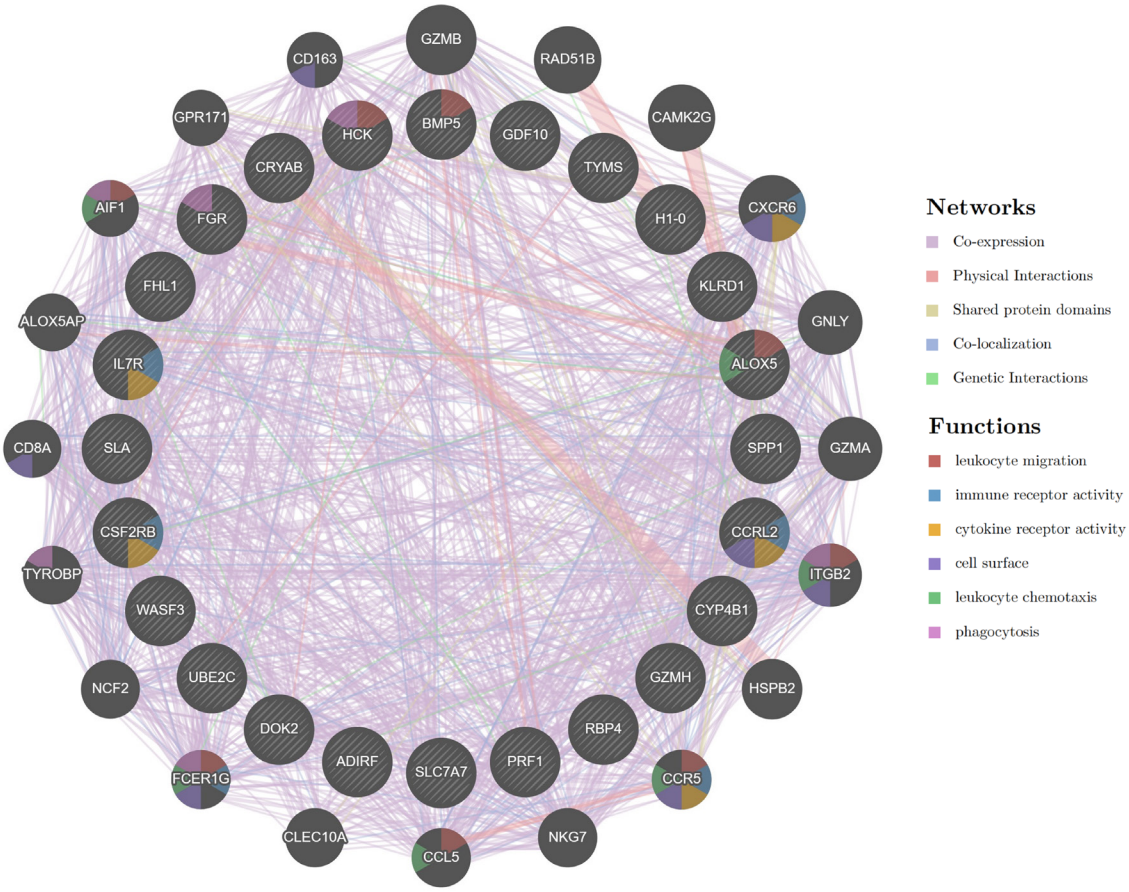


Fig. 7. GeneMANIA Analysis of 24 Common Feature Genes and Their Co-expressed Genes



Fig. 8. Enrichment Analysis of 24 Common Feature Genes (A) GO (Gene Ontology) Enrichment Results (B) KEGG (Kyoto Encyclopedia of Genes and Genomes) Enrichment Results

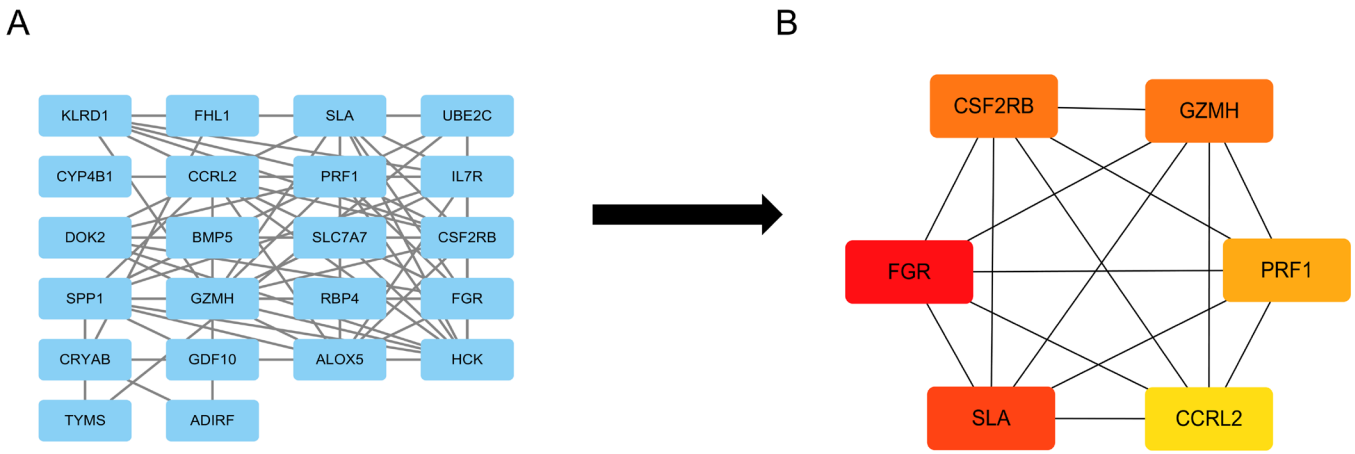


Fig. 9. Construction and Analysis of the PPI Network (A) PPI (Protein-Protein Interaction) Network Diagram (B) Top 6 Common Hub Genes Identified by MCC (Maximal Clique Centrality) Algorithm Ranking

Table 2. Basic Information of 92 Targeted Drugs Regulating the Expression of 11 Common HubGenes

Gene	Drug
ALOX5	Sulfasalazine, Zileuton, Diethylcarbamazine, Mesalamine, Meclofenamate Sodium, Pf-4191834, Balsalazide Disodium, Balsalazide, Olsalazine Sodium, Montelukast, 5-Oxo-Ete, Darbufelone, Methotrexate, Melatonin, Chembl502496, Chembl416038, Rilopirox, Tepoxalin, Atreleuton, Tenidap, Licofelone, Silybin A, Tipelukast, 6Bio, Acacetin
FGR	Tg100-801, Nintedanib, Dasatinib, Enmd-981693, Xl-228, Ilorasertib
HCK	Xl-228, Dasatinib, Bosutinib, Enmd-981693, Hesperadin, Nintedanib, Tg100-801, Ilorasertib, Pf-00562271, Doramapimod, Gefitinib, Masitinib, Chembl406845, Dovitinib, R-406, Mln-8054, Imatinib Mesylate, Ast-487
KLRD1	Etanercept, Infliximab, Methotrexate, Adalimumab
TYMS	Raltitrexed, Pemetrexed, Capecitabine, Floxuridine, Fluorouracil, Tegafur, Methotrexate, Thymidine Monophosphate, Leucovorin, Azacitidine, Prednisone, Etoposide, Eniluracil, Osi-7904, Topotecan, Tamoxifen, Hydrocortisone, Vincristine, Deoxyuridine Monophosphate, Cytarabine, Verapamil, Reserpine, Cisplatin, Dexamethasone, Carbogen, Platinum, Phentolamine, Arfolitixorin, Doxifluridine, Irinotecan
SPP1	Ask-8007, Calcitonin, Alteplase, Wortmannin, Gentamicin, Tacrolimus
RBP4	Fenretinide, Rosiglitazone
PRF1	Aldesleukin, Emapalumab
CSF2RB	Sargramostim, Talacotuzumab, Leridistim, Tagraxofusp
CYP4B1	Thalidomide, Docetaxel
BMP5	Escitalopram

as characteristic markers for diagnosing both diseases, namely ADIRF, ALOX5, BMP5, CCRL2, CRYAB, CSF2RB, CYP4B1, DOK2, FGR, FHL1, GDF10, GZMH, H1F0, HCK, IL7R, KLRD1, PRF1, RBP4, SLA, SLC7A7, SPP1, TYMS, UBE2C, and WASF3. Utilizing the MCC algorithm, we further pinpointed the top six characteristic genes: FGR, SLA, GZMH, CSF2RB, PRF1, and CCRL2. The GO and KEGG pathway enrichment analyses highlighted the significant roles of ossification, cytokine pathways, and immune pathways in both diseases.

SLA has been identified as a potential prognostic marker for pulmonary malignancies, particularly in adenocarcinomas [12]. However, the role of SLA in the pathogenesis of rheumatoid arthritis (RA) remains unclear and warrants further experimental research. In proteomic analysis of extracellular vesicles (EVs) isolated from the plasma of patients with metastatic urothelial carcinoma (mUC), GZMH was identified as one of the potential protein biomarkers associated with progression-free survival (PFS) and optimal treatment response [13]. Single-cell sequencing analysis has suggested a close association of GZMH with the development of RA [14]. CSF2rB is a promising prognostic marker for pulmonary malignancies, potentially serving as a target for cancer treatment and prevention [15]. Its role in RA, however, is not yet clear. PRF1 has been shown to be a prognostic marker associated with immune infiltration in head and neck squamous cell carcinoma [16]. Another study identified three genes closely associated with RA in CD8+ T cells: CD8A, GZMA, and PRF1 [17]. FGR, a non-receptor tyrosine kinase, is involved in the pathogenesis of various diseases, including inflammatory diseases, autoimmune disorders, and cancer immune evasion [18]. Single-cell multi-omics analysis revealed significant differential expression of FGR between malignant cells and normal epithelial cells in lung adenocarcinoma (LUAD). High expression of FGR is associated with poor prognosis in LUAD patients [19]. The pathogenic role of FGR in

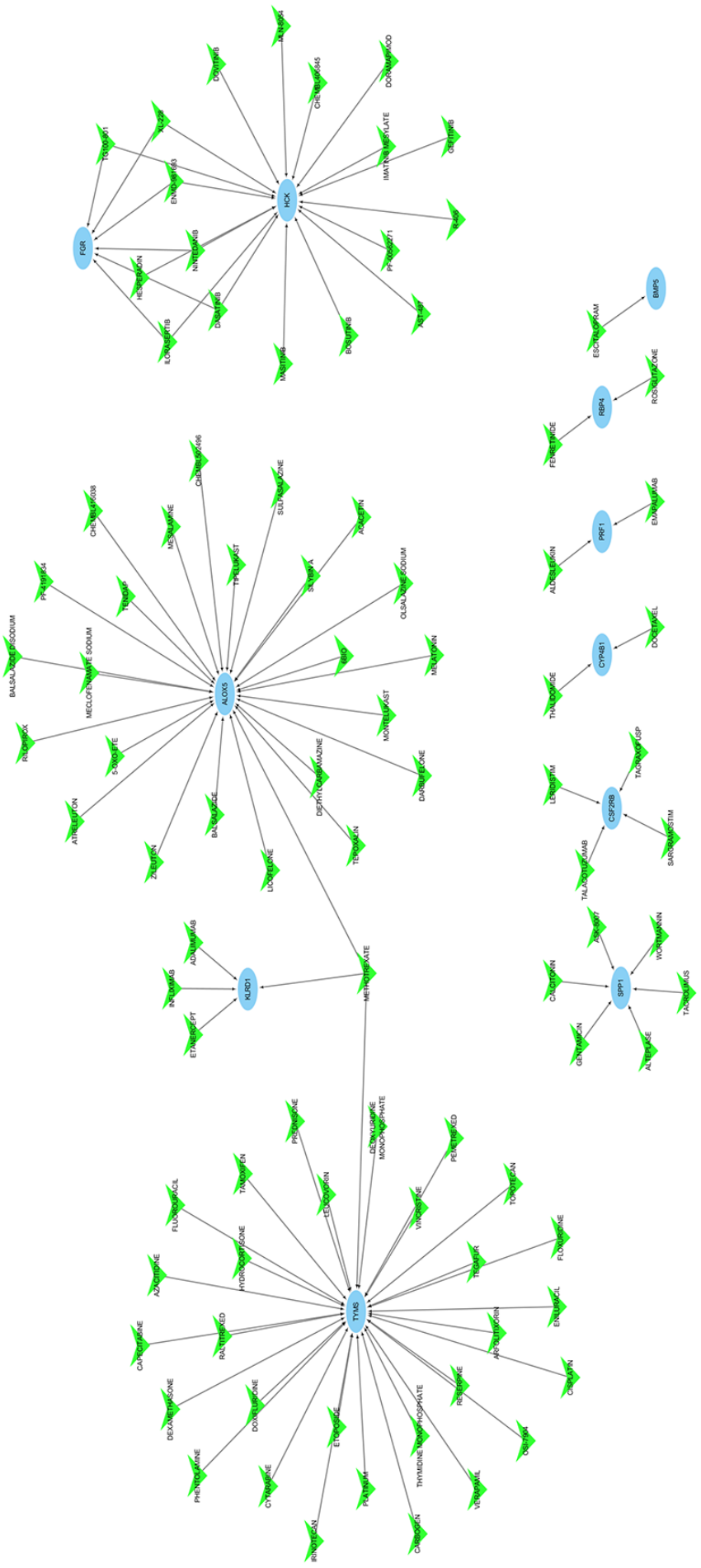


Fig.10. Prediction of Targeted Drugs for Common Hub Genes; 92 targeted drugs potentially regulating the expression of 11 common Hub Genes were predicted using the DGIdb (Drug-Gene Interaction Database), leading to the construction of a Drug-Gene Regulatory Network.

RA remains to be elucidated through further experimental research. CCRL2, a non-classical chemokine receptor belonging to the seven-transmembrane receptor family [20], plays a key role in anti-lung tumor immune responses [21]. Specialized pulmonary capillary endothelial cell expression of CCRL2 controls the directed migration of NK cells in lung cancer [22]. Reports on the role of CCRL2 in the pathogenesis of RA are scarce, necessitating further investigation.

Methotrexate, an antimetabolite drug, inhibits DNA synthesis, thereby preventing the proliferation of cancer cells. It also reduces leukocyte infiltration and lymphocyte activity, inhibiting immune evasion in lung cancer [23]. Methotrexate alleviates joint pain and swelling in RA patients by reducing inflammation and controlling immune responses [24]. Thalidomide, an immunomodulatory and antiangiogenic drug, inhibits angiogenesis, restricting the blood supply to lung cancer cells and thus hindering their growth and spread. Additionally, it enhances the attack of the immune system on cancer cells, suppressing immune evasion in lung cancer [25]. In the treatment of RA, it modulates immune responses and reduces the release of inflammatory mediators, effectively alleviating joint pain and swelling in patients [26]. Despite the potential efficacy of these drugs in treating lung cancer and RA, their toxicity limits their application. Current research directions include determining the optimal dosage and treatment regimen to achieve therapeutic effects while minimizing adverse reactions.

In summary, we identified 24 common hub genes for lung cancer and rheumatoid arthritis, with the top six ranked by the MCC algorithm being FGR, SLA, GZMH, CSF2RB, PRF1, and CCRL2. This study opens avenues for further exploration of the common pathogenesis of lung cancer and rheumatoid arthritis. However, further in vivo and in vitro experimental validation and support are required.

ABREVIATIONS

ABREVIATIONS

LC- Lung Cancer

MR – Multiple randomization

RA- Rheumatoid Arthritis

TQ – test of quality

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AUTHORS' CONTRIBUTION

CMD,CHW – Writing draft; analysis, data management

ZCS, LC – Writing draft; analysis, data visualization

QQD, WX – Writing draft; analysis, data management

XH- Conceptualisation, analysis, data management, final aproval.

All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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