Sains Malaysiana 53(12)(2024): 3895-3906
http://doi.org/10.17576/jsm-2024-5312-05

Unveiling Common Pathways and Potential Drug Targets for Ulcerative Colitis and IgG4-Related Disease through Bioinformatics Analysis

(Mendedahkan Laluan Biasa dan Sasaran Dadah Berpotensi untuk Kolitis Ulseratif dan Penyakit Berkaitan IgG4 melalui Analisis Bioinformatik)

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Received: 16 July 2024/Accepted: 8 October 2024

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ABSTRACT

Patients with ulcerative colitis (UC) are at an increased risk of developing IgG4 related diseases (IgG4-RD). However, the molecular mechanisms are not known. This study aimed to investigate the potential molecular mechanisms and drugs to treat both UC and IgG4-RD. GSE42911 and GSE40568 datasets were intersected to generate common differentially expressed genes (DEGs). The DEGs were then subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. After a protein-protein interaction network (PPI) analysis, hub genes and transcriptional regulators (TFs) were tracked. Finally, potential therapeutic drugs were predicted by the DGIDB drug database. A total of 212 common DEGs were identified in between UC and IgG4-RD. Functional enrichment revealed DEGs enriched in 'cytoplasm', and 'RNA binding'. Furthermore, KEGG pathway analysis identified significant enrichment in 'Hippo signaling'. The PPI network was enriched with 162 genes/nodes and 532 edges. Additionally, hub genes and associated with 41 TFs and 18 miRNAs were found. Finally, 16 potential drugs targeted to four hub genes were found. In summary, these findings provide novel insights into the pathophysiology of UC and IgG4-RD, highlighting potential molecular targets and drug candidates for therapeutic intervention. The identified drugs could pave the way for targeted therapies, potentially improving clinical outcomes for patients suffering from these conditions and offering a new direction for treatment strategies in both UC and IgG4-RD.

Keywords: Bioinformatics; drug molecule; IgG4 related diseases; protein-protein interaction; ulcerative colitis

ABSTRAK

Pesakit dengan kolitis ulseratif (UC) mempunyai risiko yang lebih tinggi untuk mendapat penyakit berkaitan IgG4 (IgG4-RD). Walau bagaimanapun, mekanisme molekulnya tidak diketahui. Penyelidikan ini bertujuan untuk mengkaji mekanisme molekul dan dadah yang berpotensi untuk merawat kedua-dua UC dan IgG4-RD. Dataset GSE42911 dan GSE40568 bersilang untuk menghasilkan gen biasa terekspres secara berbeza (DEG). DEG kemudiannya tertakluk kepada analisis Ontologi Gen (GO) dan Ensiklopedia Gen dan Genom Kyoto (KEGG). Selepas analisis rangkaian interaksi protein-protein (PPI), gen hab dan pengawal selia transkrip (TF) telah dijejaki. Akhirnya, dadah terapeutik yang berpotensi telah diramalkan oleh pangkalan data dadah DGIDB. Sebanyak 212 DEG biasa dikenal pasti antara UC dan IgG4-RD. Pengayaan berfungsi menunjukkan DEG yang diperkaya dalam 'sitoplasma' dan 'pengikatan RNA'. Tambahan pula, analisis laluan KEGG mengenal pasti pengayaan yang ketara dalam 'Isyarat Hippo'. Rangkaian PPI telah diperkaya dengan 162 gen/nod dan 532 segi. Selain itu, gen hab dan dikaitkan dengan 41 TF dan 18 miRNA ditemui. Akhirnya, 16 dadah berpotensi yang disasarkan kepada empat gen hab ditemui. Ringkasnya, penemuan ini memberikan pandangan baharu tentang patofisiologi UC dan IgG4-RD, menonjolkan sasaran molekul yang berpotensi dan calon dadah untuk campur tangan terapeutik. Dadah yang dikenal pasti boleh membuka jalan untuk terapi bersasar yang berpotensi meningkatkan hasil klinikal untuk pesakit yang mengalami keadaan ini dan menawarkan arah baharu untuk strategi rawatan dalam kedua-dua UC dan IgG4-RD.

Kata kunci: Bioinformatik; interaksi protein-protein; kolitis ulseratif; molekul dadah; penyakit berkaitan IgG4

INTRODUCTION

Ulcerative colitis (UC), a long-term inflammatory disorder, targets the colon and rectum, causing inflammation and ulcerations in the large intestine's lining (Du & Ha 2020). UC can be diagnosed through several methods, including colonoscopy, biopsy, and blood tests (Ungaro et al. 2017). Each of these methods has limitations. For instance, colonoscopy requires specialized equipment and expertise, biopsy may yield false-negative results, and blood tests may not provide a definitive diagnosis. The treatment of UC typically involves the use of a combination of medications, including anti-inflammatory drugs, immunosuppressants, and biologic agents (Segal, LeBlanc & Hart 2021). However, these treatments may have side effects, such as an increased risk of infection, and may not be effective for all patients. In more severe cases, surgery may be necessary to remove the affected part of the colon. Thus, individualized diagnose and treatment must be developed based on the patient's specific symptoms and disease severity.

As a systemic disorder, UC often involves multiple organ systems, including the immune system. IgG4-related disease (IgG4-RD) is a condition characterized by a high concentration of IgG4, a type of immunoglobulin G, and the accumulation of IgG4-positive plasma cells in several organs, resulting in tissue destruction and impairment (Umehara et al. 2012). The identification of IgG4-RD necessitates a joint evaluation of clinical, imaging, and microscopic data. However, these diagnostic methods have limitations, such as the potential for sampling errors, false-negative results, and the lack of standardized criteria. Glucocorticoids, azathioprine, and rituximab are used to manage IgG4-RD, aiming to reduce inflammation and stop any further harm to organs. However, these treatments may have side effects, including an increased risk of infection, hyperglycemia, and osteoporosis, and they may not be effective for all patients. Therefore, individualized treatment plans should be developed based on the patient's specific symptoms and disease severity.

Several investigations have proposed that UC sufferers may have a higher likelihood of developing IgG4-RD (Koizumi et al. 2013). However, the relationship between IgG4-RD and UC remains unclear and requires further exploration. Identifying shared molecular mechanisms between these diseases is crucial, as it may lead to a better understanding of their pathogenesis and unveil novel therapeutic targets. In particular, the identification of common pathways could highlight critical biological processes involved in both conditions, providing insight into potential therapeutic strategies. To explore the potential connection between these two diseases, we conducted a bioinformatics study. We collected two datasets, GSE42911 (from patients with UC) and GSE40568 (from patients with IgG4-RD), from the Gene Expression Omnibus (GEO) database. We identified common differentially expressed genes (DEGs) and performed pathway and enrichment analyses to gain a deeper understanding of the biological functions shared by UC and IgG4-RD. By showing the overlapping pathways, we aim to shed light on the molecular crosstalk between these diseases, which could be pivotal in developing novel treatment strategies. From the identified DEGs, we constructed a network to determine hub genes and traced transcriptional regulators. We further extracted hub genes to predict potential drugs for treating both UC and IgG4-RD (Figure 1). Our study identified several drugs with therapeutic potential for both conditions. However, further research is necessary to elucidate the precise mechanisms linking these diseases and to confirm the therapeutic relevance of these findings.

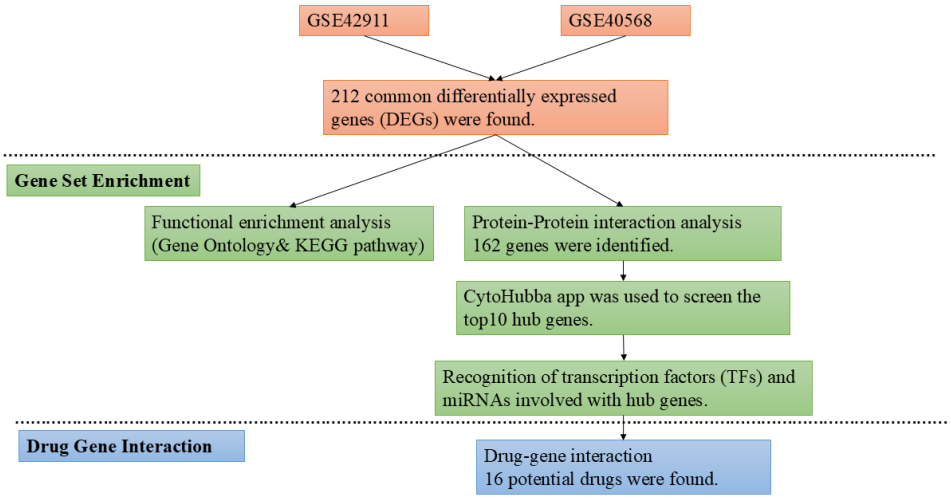

FIGURE 1. The flowchart of the study

MATERIALS AND METHODS

DATA COLLECTION

The UC dataset, GSE42911, includes five blood samples from UC patients and five normal control samples. This dataset was generated using the GPL15207 platform. GSE42911 was selected for this study because it provides comprehensive gene expression profiles from blood samples of UC patients, offering valuable insight into systemic molecular changes associated with the disease. Blood samples are especially useful in identifying biomarkers and potential therapeutic targets since they reflect disease activity and can be easily accessed in clinical settings.

The IgG4-RD dataset, GSE40568, consists of five IgG4-RD samples and three normal control samples, generated using the GPL570 platform. GSE40568 was chosen because it contains gene expression data specific to IgG4-RD, which is a relatively rare and less understood disease. The availability of matched normal controls in this dataset enhances its value for differential expression analysis, facilitating the identification of disease-specific molecular mechanisms. By intersecting the gene expression data from both datasets, we aimed to uncover common molecular pathways that could be relevant to both UC and IgG4-RD, potentially leading to new therapeutic strategies for these diseases.

DATA PROCESSING

To detect DEGs between UC and IgG4-RD samples, the GEO2R online tool was employed. GEO2R is a robust and widely-used platform that facilitates comparisons between groups of samples in the Gene Expression Omnibus (GEO) repository, using the limma (linear models for microarray data) R package. The criteria for selecting significant DEGs were set at |log fold change (logFC)| > 1 and adjusted P-value < 0.05. These thresholds ensure that only genes with biologically relevant expression changes and high statistical significance are selected, minimizing the likelihood of false positives. To identify overlapping DEGs between the two datasets (UC and IgG4-RD), a Venn diagram tool was utilized, enabling us to focus on common genes that may play a role in both diseases.

GENE ONTOLOGY AND PATHWAY ENRICHMENT ANALYSIS

To gain insights into the biological functions and pathways involved in the identified DEGs, we performed GO and KEGG enrichment analyses using the DAVID (Database for Annotation, Visualization, and Integrated Discovery) 6.8 online platform. DAVID is widely used for gene functional annotation, providing a comprehensive understanding of the biological significance of DEGs. For the analysis, we selected 'OFFICIAL GENE SYMBOL' as the gene identifier and specified 'Homo sapiens' as the species. GO analysis categorizes DEGs into three functional domains: biological process (BP), molecular function (MF), and cellular component (CC), helping us understand their roles in specific cellular contexts. KEGG pathway analysis was performed to identify metabolic and signaling pathways significantly associated with the DEGs, providing clues about the shared molecular mechanisms between UC and IgG4-RD. A P-value < 0.05 was set as the threshold for statistical significance, ensuring that only the most relevant and significant pathways were considered.

PROTEIN-PROTEIN INTERACTION (PPI) NETWORK AND HUB GENE EXTRACTION

To further investigate the interactions between DEGs in UC and IgG4-RD, we constructed a protein-protein interaction (PPI) network using the STRING database. STRING is a well-established resource for predicting protein-protein interactions, including both direct physical interactions and indirect functional associations. A confidence score of ≥0.4 was used as the threshold to filter significant interactions, which provides a balance between sensitivity and specificity in identifying relevant connections. The PPI network was visualized using Cytoscape software (v3.7.1), a powerful tool for network analysis and visualization. To identify the most critical genes within the network, we applied the CytoHubba plugin, which ranks nodes based on various topological parameters. The top 10 hub genes, which are expected to play key roles in the pathogenesis of both diseases, were selected based on their connectivity and centrality within the PPI network.

RECOGNITION OF HUB GENES ASSOCIATED TRANSCRIPTION FACTORS AND miRNAs

To govern the expression of genetic information, proteins called transcription factors (TFs) bind to specific gene sequences. We used the NetworkAnalyst platform and accessed the JASPAR database to identify topologically credible TFs that tend to bind to our hub genes. JASPAR is a free and publicly available TF database that collects the binding sites of TFs to DNA and can be used to predict the binding regions of TFs to sequences (Fornes et al. 2020). NetworkAnalyst is a web-based visualization tool designed for meta-analyzing gene expression information and conducting protein interaction analysis (Zhou et al. 2019). To trace miRNAs that negatively affect protein expression by targeting gene interactions, we incorporated miRNAs into our analysis. The miRNAs were extracted from the comprehensive validity database for miRNA-target gene interactions, mirTarbase, based on their interaction with hub genes focused on topological analysis.

EVALUATION OF APPLICANT DRUGS

To identify potential therapeutic agents, we used the Drug-Gene Interaction Database (DGIDB), an online resource that links genes to known drug interactions based on data from multiple sources, including FDA-approved drugs and experimental compounds. We specifically searched for drugs or compounds that interact with the identified hub genes. This approach allows us to explore existing drugs that could potentially be repurposed to treat both UC and IgG4-RD. By cross-referencing our hub genes with the drug-target data available in DGIDB, we generated a list of candidate drugs that may hold therapeutic potential. This drug prediction step is crucial for identifying compounds that could be tested in future preclinical or clinical studies, facilitating the translation of our findings into actionable therapeutic strategies.

STATISTICS ANALYSIS

To ensure the reliability of the differential expression analysis, a moderated t-test was performed using the limma package in GEO2R, which accounts for multiple testing by adjusting the P-values with the Benjamini-Hochberg procedure to control the false discovery rate (FDR). Only DEGs with an adjusted P-value < 0.05 and $|\log FC| > 1$ were considered statistically significant, ensuring a balance between the discovery of meaningful genes and minimizing false positives. Additionally, statistical analysis for pathway enrichment and network analysis was conducted using appropriate tools, with significance set at P-value < 0.05. All analyses were performed using built-in functions and libraries provided by the respective platforms to ensure consistency and accuracy in data interpretation.

RESULTS

IDENTIFICATION OF COMMON DEGs BETWEEN UC AND IgG4-RD

In the UC dataset, 2461 genes were identified as differentially expressed, with 1441 up-regulated and 1020 down-regulated. In the IgG4-RD dataset, 2008 genes were identified as differentially expressed, with 1291 up-regulated and 717 down-regulated. Using a Venn diagram analysis, 212 genes were found to overlap between the two datasets, with 187 up-regulated and 25 down-regulated. The common DEGs extracted are displayed in Figure 2.

GENE ONTOLOGY AND PATHWAY ENRICHMENT ANALYSIS

The Gene ontology (GO) analysis comprised three aspects: Cellular Component (CC), Biological Process (BP), and Molecular Function (MF). BP annotation showed significant enrichment in 'positive regulation of transcription from RNA polymerase II promoter', 'signal transduction', and 'negative regulation of gene expression', while CC annotation was enriched in 'cytoplasm', 'membrane', 'nucleoplasm', 'nucleus', 'plasma membrane', 'extracellular exosome', and 'cytosol'. The MF annotation showed enrichment in 'identical protein binding', 'protein binding', and 'RNA binding'. Furthermore, KEGG pathway analysis identified significant enrichment in 'Hippo signaling', 'Lysosome', 'Fc gamma R-mediated phagocytosis', 'Cortisol synthesis and secretion', and 'Hippo signaling pathway-multiple species' (Figure 3).

THE PPI AND HUB GENES ANALYSIS

Figure 4(A) illustrates the up-regulated genes with yellow nodes and down-regulated genes with blue ones. The PPI network was enriched with 162 genes/nodes and 532 edges. Figure 4(B) presents the top 10 hub genes: APP, CREB1, YAP1, PPP1CB, PAPOLA, SRSF1, EPS8, RAC1, HMGB1, and RAB11A, which could be potential drug targets.

CONSTRUCTION OF REGULATORY NETWORKS

The relationship between TF regulators and top 10 hub genes was depicted in Figure 5(A), while the relationship between miRNA regulators and top 10 hub genes was pictured in Figure 5(B). The regulatory networks showed that 41 TFs and 18 miRNA regulatory molecules were involved in the regulatory process of hub genes.

THE DRUG-GENE INTERACTION

The top 10 genes were submitted to the DGIDB database in order to evaluate the drugs. These drugs are recommended for both two diseases. Table 1 shows the 16 potential drugs and their corresponding genes.

DISCUSSION

Ulcerative colitis (UC) is frequently associated with multiple organ disorders. While IgG4 infiltration may be detected in the colonic mucosa (Koizumi et al. 2013), the infiltration of IgG4 and tissue fibrosis are characteristic of IgG4-related disease (IgG4-RD). Some studies have suggested an increased risk of IgG4-RD in patients with UC (Kuwata et al. 2014; Lindo Ricce et al. 2016). However, the relationship between IgG4-RD and UC is not fully understood. This study aimed to clarify the potential interactions between UC and IgG4-RD and identify potential drugs for treatment by bioinformatics methods.

Bioinformatics is an interdisciplinary field that leverages computational methods and tools to analyze and interpret biological data. It plays a pivotal role in processing and understanding large-scale genetic, protein, and other molecular data, contributing significantly to areas such as genomics, proteomics, and disease research (Akalin 2006). In the context of UC (Yang et al. 2024) and IgG4-RD (Lu et al. 2023), bioinformatics is particularly

TABLE 1. The candidate drugs and corresponding genes for UC and IgG4-RD

Gene	Drug
APP	GENTIAN VIOLET
APP	HYDROXYCHLOROQUINE
APP	PROPOFOL
APP	DAUNORUBICIN
RAC1	VEMURAFENIB
RAC1	DABRAFENIB
CREB1	NICOTINE
CREB1	CITALOPRAM
CREB1	ALCOHOL
HMGB1	UREA
HMGB1	SODIUM CHLORIDE
HMGB1	PREDNISOLONE
HMGB1	CISPLATIN
HMGB1	AMPICILLIN
HMGB1	ITRACONAZOLE
HMGB1	ETOPOSIDE

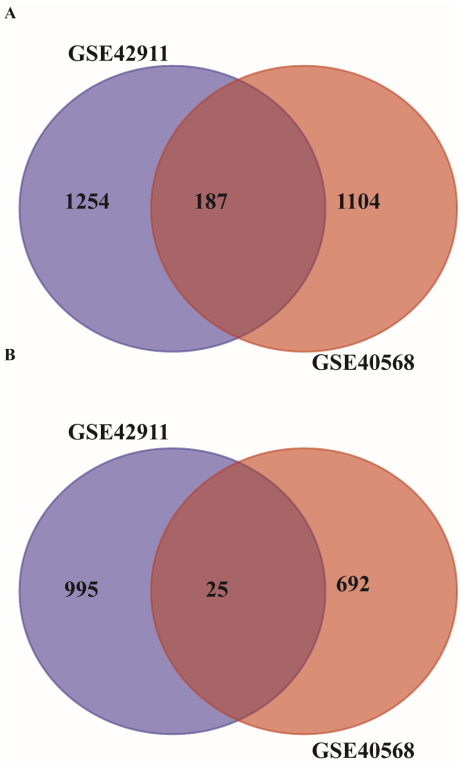

FIGURE 2. Common differentially expressed genes (DEGs) identification for ulcerative colitis (UC) and IgG4 related diseases (IgG4-RD). (A) 187 common DEGs with up-regulation between UC and IgG4-RD. (B) 25 common DEGs with down-regulation between UC and IgG4-RD

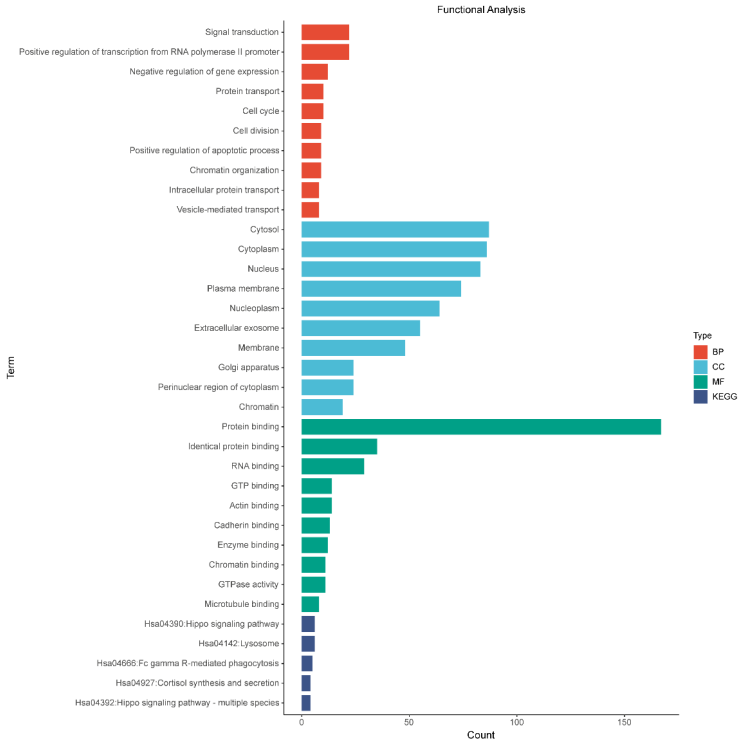

FIGURE 3. Functional analyses of differentially expressed genes (DEGs) between ulcerative colitis (UC) and IgG4 related diseases (IgG4-RD). Red, blue, green, and dark indicating biological process (BP), molecular function (MF), and cellular component (CC), and KEGG pathway analyses, separately

valuable, as biomarkers like serum IgG4 levels and inflammatory markers (IL-2 receptor and CCL18) can aid in diagnosing and monitoring disease activity. In this study, we identified 212 common DEGs by bioinformatics between the two diseases, which may play crucial roles in their pathogenesis.

The GO database is one of the most widely used resources for annotating gene function. In our study, for BP annotation, the top enriched term was 'signal transduction'. For CC analysis, the DEGs were significantly enriched in locations such as the cytosol, cytoplasm, nucleus, nucleoplasm, extracellular exosome, and membrane. Regarding MF, 'protein binding' and 'RNA binding' were the most prominent terms. KEGG pathway analysis, a commonly used method to associate gene function with biological pathways, integrates genomic and functional data to provide deeper insights into molecular mechanisms. In this study, the top pathways identified were Hippo signaling and Fc gamma R-mediated phagocytosis. The Hippo pathway has been shown to play a role in immune modulation (Xie et al. 2021), which could be relevant to the pathogenesis of both UC and IgG4-RD. Additionally, Fc gamma receptors, which bind the Fc portion of IgG, activate monocytes and regulate inflammatory responses (Kusner, Hall & Jackson 1999), further suggesting a link to the immune processes involved in these diseases.

To explore the biological signatures at the protein level, we constructed a PPI network using the identified DEGs. This analysis resulted in a network consisting of 162 genes connected by 532 edges. From this network, we identified the top ten key genes: APP, CREB1, YAP1, PPP1CB, PAPOLA, SRSF1, EPS8, RAC1, HMGB1, and RAB11A. These genes hold potential as drug targets or biomarkers, offering valuable insights for future research on both UC and IgG4-RD.

APP is a transmembrane protein that is involved in the production of amyloid-β (Cho et al. 2022), although its expression in other tissues is not well understood. CREB has the potential to influence the production of inflammatory cytokines (Fouad et al. 2021), which could be a factor in the emergence of UC. Additionally, CREB is involved in the up-regulation of mtROS (Zhu et al. 2022), which may be involved in IgG4-related sialadenitis. YAP1 is a transcriptional co-activator of the Hippo pathway and controls cell proliferation and differentiation (Deng et al. 2018). It may have therapeutic potential as a preventative target for UC. SRSF1 may be a factor in the regulation of both signaling and cytokine production in human T

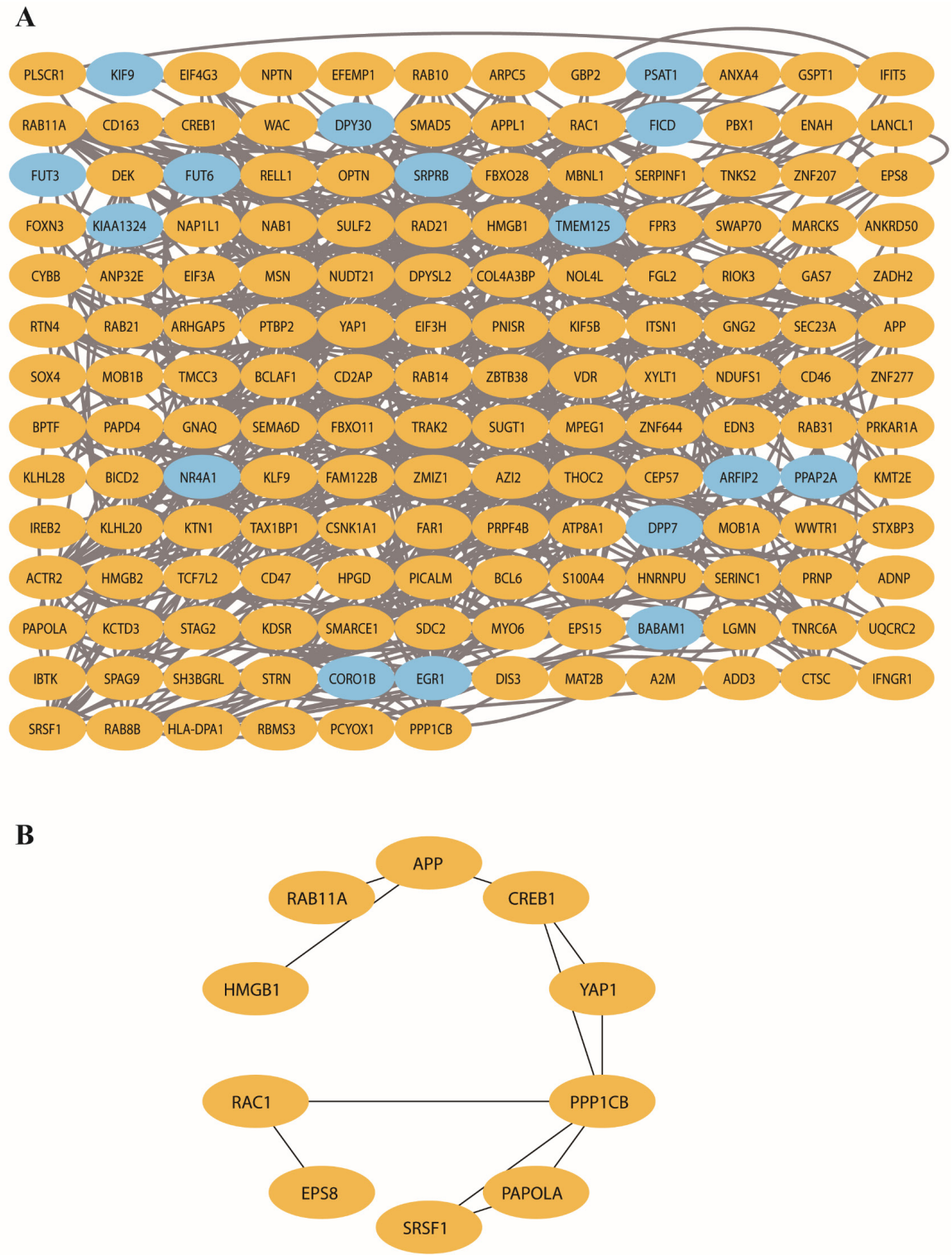

FIGURE 4. Protein-protein interaction network (A) and hub genes (B). Yellow ellipses stand for up-regulation gene, while blue ellipses for down-regulation

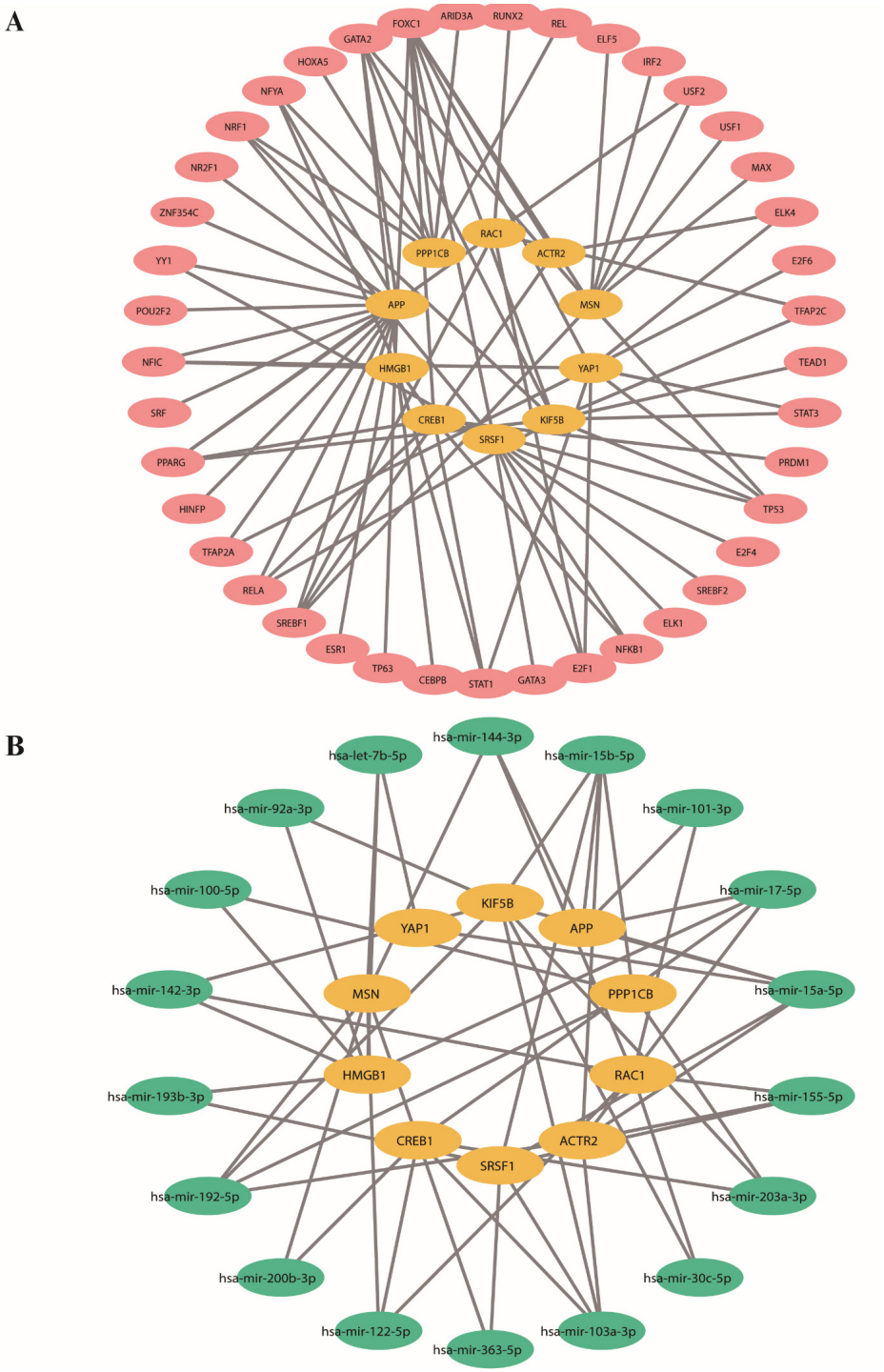

FIGURE 5. (A) The hub genes and transcription factors (TFs) interaction network. Yellow ellipses represent hub genes, while pink represents TFs, and (B) miRNAs interactions with hub genes. Green represents miRNAs, yellow indicates hub genes

cells (Katsuyama et al. 2020), potentially influencing the immunity of B cells in UC and IgG4-RD (Long et al. 2020). RAC1, belonging to the Rho GTPase family, has been found to facilitate the maturation and movement of dendritic cells (Kanauchi et al. 2022), potentially leading to an improvement in UC symptoms. It is also involved in Fc receptor-mediated phagocytosis, which is related to IgG4-SC (Zhang et al. 2005). HMGB1 is a nuclear protein that, when released into the extracellular space, can contribute to inflammatory responses and the induction of UC (Chen et al. 2020). It may also alter the subcellular distribution of autoantigens and be involved in IgG4-RD (Sanford, Dietzmann & Sullivan 2005). These hub genes have the potential to be biomarkers and drug targets for UC and IgG4-RD.

The DEGs were also used to construct a TFs-genes and miRNAs interaction network to investigate the biological mechanisms at both the transcriptional and post-transcriptional levels. TFs regulate the transcriptional efficiency of their target genes, while miRNAs inhibit post-transcriptional gene expression by specifically binding to target mRNA. In our analysis, we identified several key TFs, including RUNX2, REL, ELF5, IRF2, USF2, USF1, MAX, ELK4, and CEBPB. Notably, REL is a mediator of the NF-κB inflammatory signaling pathway, which has been implicated in UC. Additionally, CEBPB, STAT1, and REL play significant roles in UC-associated inflammation (Janse et al. 2011; Nowak et al. 2022), further supporting their relevance to the pathogenesis of UC. USF1 and USF2 may participate in the dysregulated expression of the polymeric immunoglobulin receptor in UC (Bruno et al. 2004). In addition, STAT3, ESR1, RELA, PPARG, and NFR1 have been considered as potential therapeutic targets for UC (Luo et al. 2020; Qin et al. 2017; Singh et al. 2022). Meanwhile, SREBP2 and ELK1 have been shown to regulate the inflammation of colon epithelium (Park et al. 2016). NF-KB1, TP63, SRF, TP53, and E2F1 are also strongly associated with UC (Ikeda et al. 2018; Lees et al. 2011; Maden & Acuner 2021). Furthermore, REL is involved in CD40-dependent activation of IgG4, while STAT3 is involved in germinal center formation and fibrosis in the development of IgG4-RD (Jiang et al. 2020). B lymphocyte-induced maturation protein 1, is upregulated in the peripheral blood of IgG4-RD patients, probably by inhibiting the differentiation of follicular helper T cells (Chen et al. 2018). Additionally, GATA3 is involved in lymphocytic recruitment in IgG4-RD (Zen et al. 2013). We also identified miRNAs associated with the common DEGs, including mir-103a-3p, mir-200b-3p, mir-192-5p, and mir-142-3p, which have been shown to play roles in the treatment of UC (Lu et al. 2021; Zhao et al. 2022; Zheng, Lu & Fan 2021).

A drug-gene network was constructed to identify potential drugs for both UC and IgG4-RD. Currently, 5-aminosalicylic acid (5-ASA) is a primary therapy for UC, while glucocorticoids are used if 5-ASA fails to induce remission. Glucocorticoids are also a primary treatment for IgG4-RD. Immunomodulators such as azathioprine, methotrexate, and cyclophosphamide are suggested as additions to the regimen (Lanzillotta et al. 2021). Given the increasing incidence of both UC and IgG4-RD, there is a need to identify novel treatments for both diseases. Nicotine has been shown to have beneficial effects on UC by regulating microRNA-124 and STAT, and by reducing the expression of CREB, which is associated with IgG4-related sialadenitis (Pandey et al. 2001; Qin et al. 2017). Prednisolone is a common clinical therapy for both UC and IgG4-RD (Arisaka et al. 2019; Kuo, Chen & Wu 2021). Citalopram presents anti-inflammatory effects and has the potential to protect gut barrier function, while hydroxychloroquine is involved in inflammation and immunoregulation (Eyzaguirre-Velasquez et al. 2021; Saraiva-Mangolin et al. 2021).

In summary, our analysis showed potential shared functions and pathways in the DEGs of UC and IgG4-RD. The TFs, microRNAs, and drugs are known to be involved in inflammation and immunoregulation, suggesting their potential relevance to the pathogenesis of both diseases. Therefore, the identified hub genes may represent potential therapeutic targets for UC and IgG4-RD. However, it should be noted that the hub genes, regulatory network, and candidate drugs identified in this study are based on bioinformatic and systems biology analyses as well as a summary of relevant literature. More research is needed to confirm the accuracy of these findings.

CONCLUSION

We employed bioinformatics methods to investigate the correlation between UC and IgG4-RD, which resulted in the discovery of ten hub genes. Additionally, GO and KEGG pathway analyses showed significant biological processes and pathways associated with these genes. Furthermore, we explored potential medications that could target these hub genes, highlighting their therapeutic promise for UC and IgG4-RD. Overall, our findings contribute to a better understanding of the molecular mechanisms underlying the relationship between UC and IgG4-RD, and suggest avenues for future research and targeted therapy.

ACKNOWLEDGMENTS

This study was supported by Natural Science Foundation of Fujian Province (Grant NO.2022J05298). The authors contributions are as follows, Zheng Wan designed the study. Quan Liao, Fangyuan Zhou, Huasheng Lin, Xiongwei Zheng, Kaiyue Li, Zhiyun Weng, and Hongjian Zhang performed data analysis. Zheng Wan wrote the draft. All members participated in discussion. All authors approved the final manuscript. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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