Am J Clin Exp Immunol 2026;15(2):112-123
www.ajcei.us /ISSN:2164-7712/AJCEI0169839

Original Article

Shared gene signatures between rheumatoid arthritis and Sjögren's syndrome

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Received November 6, 2025; Accepted February 23, 2026; Epub April 15, 2026; Published April 30, 2026

Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune disease that can lead to multiple complications. Sjögren's syndrome (SS) is another autoimmune condition that may occur as a primary disorder or in conjunction with other autoimmune diseases, including RA. This study aimed to investigate the shared gene signatures between RA and SS. Gene expression datasets for RA (GSE15573, GSE93776) and SS (GSE48378, GSE94510, GSE93683) were obtained and analyzed to identify differentially expressed genes (DEGs) in peripheral blood mononuclear cells (PBMCs) and T cells. Gene ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed on the DEGs identified. Quantitative real-time PCR (qRT-PCR) was used to validate the expression levels of DEGs in PBMCs from patients with RA and SS. A total of 244 DEGs were identified from the RA PBMC dataset, comprising 142 upregulated genes and 102 downregulated genes. These DEGs were significantly enriched in biological processes related to immune responses, including cellular response to lipopolysaccharide, defense response against fungi, inflammatory responses, and antibacterial humoral responses. In contrast, 335 DEGs were identified from the SS PBMC dataset; among these, 320 genes were upregulated, while 15 were downregulated. The DEGs associated with SS showed strong involvement in defense responses against viruses, innate immune responses, viral responses, as well as cellular reactions to lipopolysaccharide. Moreover, we identified 12 shared DEGs between RA and SS PBMCs: RNASE2, NDUFB3, LY96, ANKRD22, EIF2AK2, RNASE3, CLEC4D, TNFAIP6, DYNLT1, RPS27L, LILRA5, and F5. Validation through qRT-PCR confirmed increased expression levels of RNASE2, RNASE3, NDUFB3, and EIF2AK2 in PBMCs. This study successfully delineated key DEGs along with their associated biological processes within the context of RA and SS PBMCs. Through bioinformatics analyses combined with qRT-PCR validation, we have identified four critical genes that may serve as potential biomarkers or therapeutic targets for further investigation.

Keywords: Rheumatoid arthritis, Sjögren's syndrome, differentially expressed genes, function analysis

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by systemic inflammation and progressive joint destruction, it primarily affects women, and its pathogenesis remains incompletely understood [1, 2]. Patients with RA have a variety of complications, such as Sjogren's syndrome (SS), pulmonary interstitial fibrosis, pericarditis, and amyloidosis. SS is a systemic autoimmune disorder characterized by destruction of exocrine glands [3, 4]. Most SS patients are middle-aged female [5], and the pathogenesis and mechanism of SS remain unclear. SS is divided into primary SS and secondary SS, in which secondary SS is often seen in RA patients and connective tissue diseases including systemic lupus erythematosus (SLE) patients [6-8]. RA patients and SS patients have many similarities. First, women are more frequent patients than men are. Second, failure in immune tolerance results in producing circulating auto-antibodies. Moreover, SS can be secondary to RA, and various similarities have been identified in the pathogenesis of RA and SS. Studies have shown that B cell activation and proliferation through BAFF are involved significantly in RA and SS [9-11]. In addition, abnormalities in T cells, both qualitative and quantitative lead to the development and exacerbation of RA and SS [12-14]. However, previous analyses have

Table 1. Summary of GEO datasets included in this study

GEO accession	Platforms	Patients	Healthy control	Samples
GSE15573	GPL6102	RA:18	15	PBMC
GSE93776	GPL570	RA:18	18	$CD4^+$ T cell
GSE93776	GPL570	RA:24	24	$CD8^+$ T cell
GSE48378	GPL5175	SS:11	16	PBMC
GSE94510	GPL570	SS:18	18	$CD4^+$ T cell
GSE93683	GPL570	SS:24	24	$CD8^+$ T cell

focused on either disease individually, so the overlapping molecular characteristics of RA and SS are poorly explored. Hence, determining the genes whose expression profiles were abnormal for both RA and SS was the key towards deciphering their possible pathogenesis. This algorithm can be useful to anticipate the incidence of secondary SS in RA patients.

Advances in high-throughput sequencing have enabled the use of transcriptome data to study gene expression profiles, identify disease markers and therapeutic targets, and detect key molecules in disease pathogenesis. Our previous research revealed shared gene signatures between SLE and SS [14, 15]. In this paper, we performed the most comprehensive investigation of gene expression datasets derived from the GEO database to mine the common differentially expressed genes (DEGs) among the RA and SS patients. And, expression levels of candidate significant DEGs were also validated by clinical samples of patients and healthy individuals. The goal of the current research was to determine the possible role of key genes taking part in the pathology of both RA and SS.

Materials and methods

Data sources and differentially expressed genes screened

Gene expression datasets for RA and SS were obtained from the Gene Expression Omnibus (GEO) database. In this study, only those datasets that included more than 10 patients and 10 controls were analyzed. Subsequently, GSE15573, GSE93776, GSE48378, GSE94510, and GSE93683 were utilized to investigate the shared differentially expressed genes (DEGs) between RA and SS patients [16-19]. Detailed information regarding these GEO datasets is presented in **Table 1**. The DEGs between patients and normal controls in each dataset were screened, using $|Log_2$ (fold change)| > 0.5 and adjusted *p*-value < 0.05 as thresholds. Then, the shared genes of these DEGs from each datasets were screened.

Function analysis for DEGs

GO and KEGG pathway analysis of the DEGs were performed by using DAVID bioinformatics Resources (https://david.ncifcrf.gov/tools.jsp) [20]. R Bubble diagrams are used for visualizing the enriched GO term and KEGG pathway.

PBMC samples collection

Blood was collected from patients with RA (n=20; Age: 48.10±12.93) and SS (n=19; Age: 47.68±12.24). RA patients were recruited from the Rheumatism and Immunology Department in Tangdu Hospital of Air Force Medical University, China, and met the criteria provided by the American College of Rheumatology in 2010. SS patients were recruited according to the classification criteria proposed by American-European Consensus Group (AECG) in 2002. The control group comprised of physical examination healthy population in the same time period (n=22; Age: 43.14±10.13). PBMCs were enriched by ficoll separation based on the supplier's instruction (TBD, Tianjin, China, Cat: LTS1077). The experimental protocol was approved by the Ethics Committee of Tangdu Hospital at Fourth Military Medical University (No. 202404-12). This study did not involve patient identification data and did not violate individual rights or interests; therefore, informed consent was waived.

Quantitative real-time PCR (qRT-PCR)

Firstly, RNA extracted from PBMCs was reverse transcribed into cDNA using a reverse transcription kit (GLPBIO, Cat: GK20008) in accordance with the manufacturer's instructions. Subsequently, quantitative real-time PCR (qRT-PCR) was conducted to assess the expression levels of differentially expressed genes (DEGs) utilizing BlasTaq™ qPCR Mastermix (Applied Biological Materials Inc., Cat: 891, Canada). The relative expression levels of the genes were normalized to GAPDH using the $2^{-\Delta\Delta Ct}$ method. All primers were listed in **Table 2**.

Table 2. Primers used for qPCR analysis

Gene	Primers sequences
RNASE2	5'-ATCAACGACGAGACCCTCCA-3'
	5'-AGGAGCTTGGCAGATGAGTG-3'
NDUFB3	5'-TCAGATTGCTGTCAGGCAGA-3'
	5'-TGCAAAGCCACCCATGTATCT-3'
LY96	5'-CATACACCTACTGTGGGAGAGA-3'
	5'-TAGGTTGGTGTAGGATGACAAAC-3'
ANKRD22	5'-TGACCTCCTGTCCACATTGC-3'
	5'-CCCATGTACCCTTCACCACA-3'
F5	5'-AGGTGAAACGTGATGACCCC-3'
	5'-AGTGCCCAGTGAAGTGGATG-3'
RNASE3	5'-GCCATCCAGCACATCAGTCT-3'
	5'-TGGTCTGTCTGCATACGTGC-3'
CLEC4D	5'-CTGATACCTTCGGTTATTGCTGT-3'
	5'-GCACTCCTGTGCCTCTCTTAC-3'
TNFAIP6	5'-TTTCTCTTGCTATGGGAAGACAC-3'
	5'-GAGCTTGTATTTGCCAGACCG-3'
DYNLT1	5'-GTGGTAACGCTTATCAACACAGC-3'
	5'-GCTTGGTGAGTTGGCTTAAAGT-3'
RPS27L	5'-AGTGGCATGATTTACCCGCA-3'
	5'-AGGCACCAGAACCACTCAAC-3'
LILRA5	5'-TCACGGCTGAGATTCGACAG-3'
	5'-CCTGCGAGAGCCATAGCATC-3'
EIF2AK2	5'-GCCGCTAAACTTGCATATCTTCA-3'
	5'-TCACACGTAGTAGCAAAAGAACC-3'
GAPDH	5'-GGTGGTCTCCTCTGACTTCAACAG-3'
	5'-GTTGCTGTAGCCAAATTCGTTGT-3'

Statistical analysis

R (version 4.3.2) was used for statistical analysis. Fold change and Student t test were used to compare the expression data between different groups. Student t test was used to analyze the differences of genes expression between patients and healthy controls, and $P < 0.05$ was considered to be statistically significant.

Results

Differentially expressed genes in RA and SS datasets

First, DEGs in PBMCs from RA and SS datasets were identified compared with normal controls, as illustrated in **Figure 1A** and **1B**. In the RA datasets, a total of 142 up-regulated and 102 down-regulated DEGs were detected. Conversely, the SS datasets revealed 320 up-regulated and 15 down-regulated DEGs.

DEGs in T cells from patients with RA and SS were also compared. In $CD4^+$ T cells, 372 up-regulated genes were detected in the RA dataset and 181 in the SS datasets respectively; there were 188 down-regulated genes detected in RA patients and 793 in SS patients (**Figure 1C** and **1D**). As far as $CD8^+$ T cells are concerned, the screening identified 534 up-regulated and 679 down-regulated genes between the RA patients; for the SS patients significant results were also present with relation to gene expression: 331 up-regulated, 382 down-regulated (**Figure 1E** and **1F**). Supplementary Table 1 includes information about the DEGs related to both RA and SS.

Function analysis of DEGs in RA

To explore the possible mechanism for the development of RA, we performed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis to evaluate the biological functions of DEGs. Firstly, in aspect of GO_BP (biological process) analysis, the DEGs PBMCs were remarkably enriched in immune response related pathways. Which were included cellular response to lipopolysaccharide, defense response to fungi, inflammatory response, and antibacterial humoral responses. Moreover, GO_MF (molecular function) analysis showed that these PBMC-DEGs mainly enriched for structural constituents of ribosomes, receptor binding to RAGE, binding to Toll-like receptor 4, lipopolysaccharide binding activities and hyd-ro-lyase activity. Moreover, KEGG analysis showed that these genes were highly related to the processes of Ribosome biogenesis, Oxidative phosphorylation and Thermogenesis (**Figure 2A**).

Moreover, DEGs of $CD4^+$ T cells were enriched in protein ubiquitination, JAK-STAT cascade and cytokine-mediated signaling pathway (GO_BP). KEGG pathway analysis showed that these DEGs were involved in JAK-STAT signaling pathway, TNF signaling pathway and Necroptosis (**Figure 2B**). With regard to DEGs of $CD8^+$ T cells, they were enriched in cell division, protein phosphorylation and regulation of transcription (GO_BP). KEGG analysis showed these DEGs were associated with Cell cycle, Ubiquitin me-

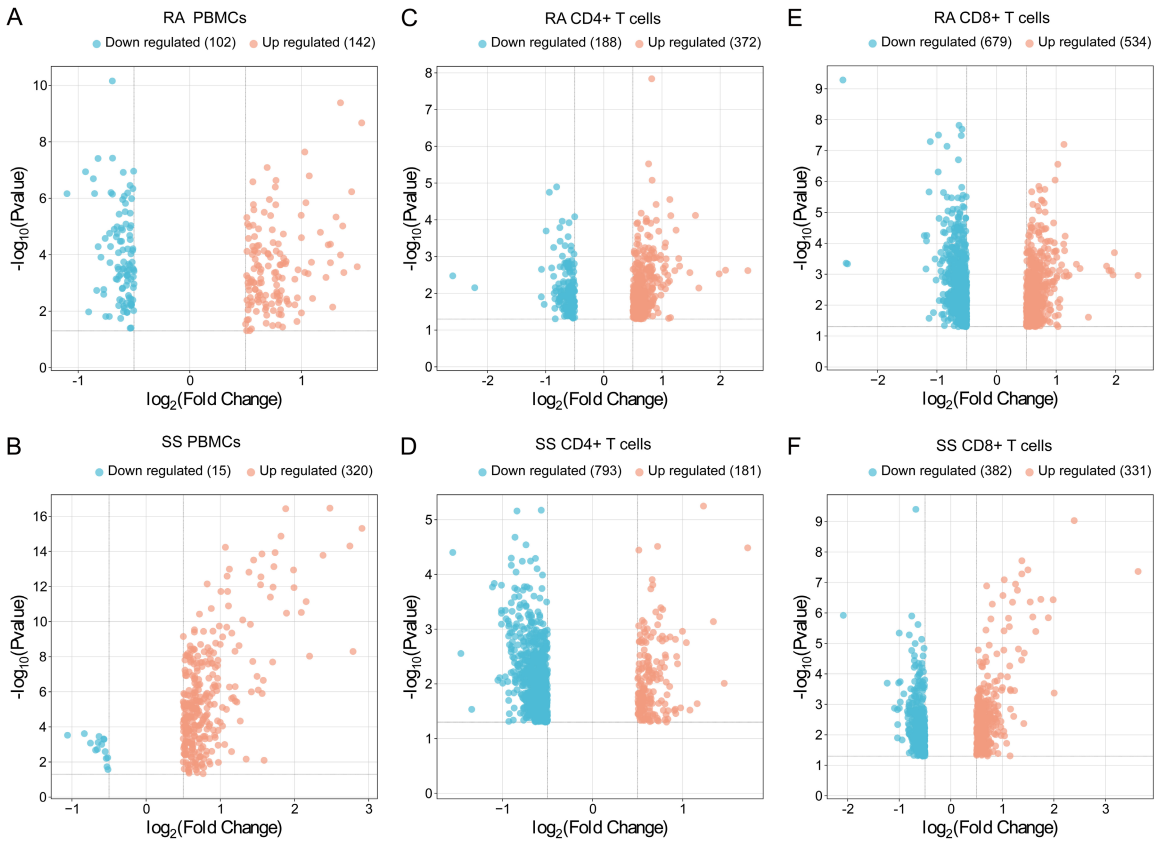

Figure 1. The differentially expressed genes (DEGs) in RA and in SS datasets. A. Volcano plot showing the expression change of DEGs in RA PBMCs dataset. B. Volcano plot showing the expression change of DEGs in SS PBMCs dataset. C, D. Volcano plot showing the expression change of DEGs in RA and SS $CD4^+$ T cells. E, F. Volcano plot showing the expression change of DEGs in RA and SS $CD8^+$ T cells.

diated proteolysis, and Cellular senescence (**Figure 2C**).

Function analysis of DEGs in SS

We conducted the GO and KEGG analysis for DEGs in SS datasets. With regard to DEGs of SS PBMC, GO_BP analysis showed that these genes were closely involved in defense response to virus, innate immune response, response to virus and cellular response to lipopolysaccharide. GO_MF showed that these DEGs were significantly related to protein binding, pattern recognition receptor activity, complement receptor activity and cytokine activity. KEGG pathway showed these DEGs were related to various of virus infections, including Influenza A, Measles, Hepatitis C and COVID-19 infection, etc (**Figure 3A**).

Moreover, the DEGs of $CD4^+$ T cells were enriched in protein modification and transport associated pathways, including protein ubiquitination, protein phosphorylation and ER to Golgi vesicle-mediated transport. KEGG pathway analysis showed that these DEGs were involved in Ubiquitin mediated proteolysis, cell cycle and autophagy (**Figure 3B**). With regard to the DEGs of $CD8^+$ T cells in SS datasets, these DEGs were enriched in response to virus, regulation of interferon-beta production, protein ubiquitination and cell cycles (**Figure 3C**).

The shared DEGs in RA and SS datasets

According to the previously set criteria for DEGs, 12 shared DEGs in RA and SS PBMC were found (RNASE2, NDUFB3, LY96, ANKRD22, F5, RNASE3, CLEC4D, TNFAIP6, DYNLT1, RPS27L, LILRA5, EIF2AK2), which were all upregulated compared to controls (**Figure 4A-C**). GO analysis indicated that these DEGs were predominantly linked to the innate immune re-

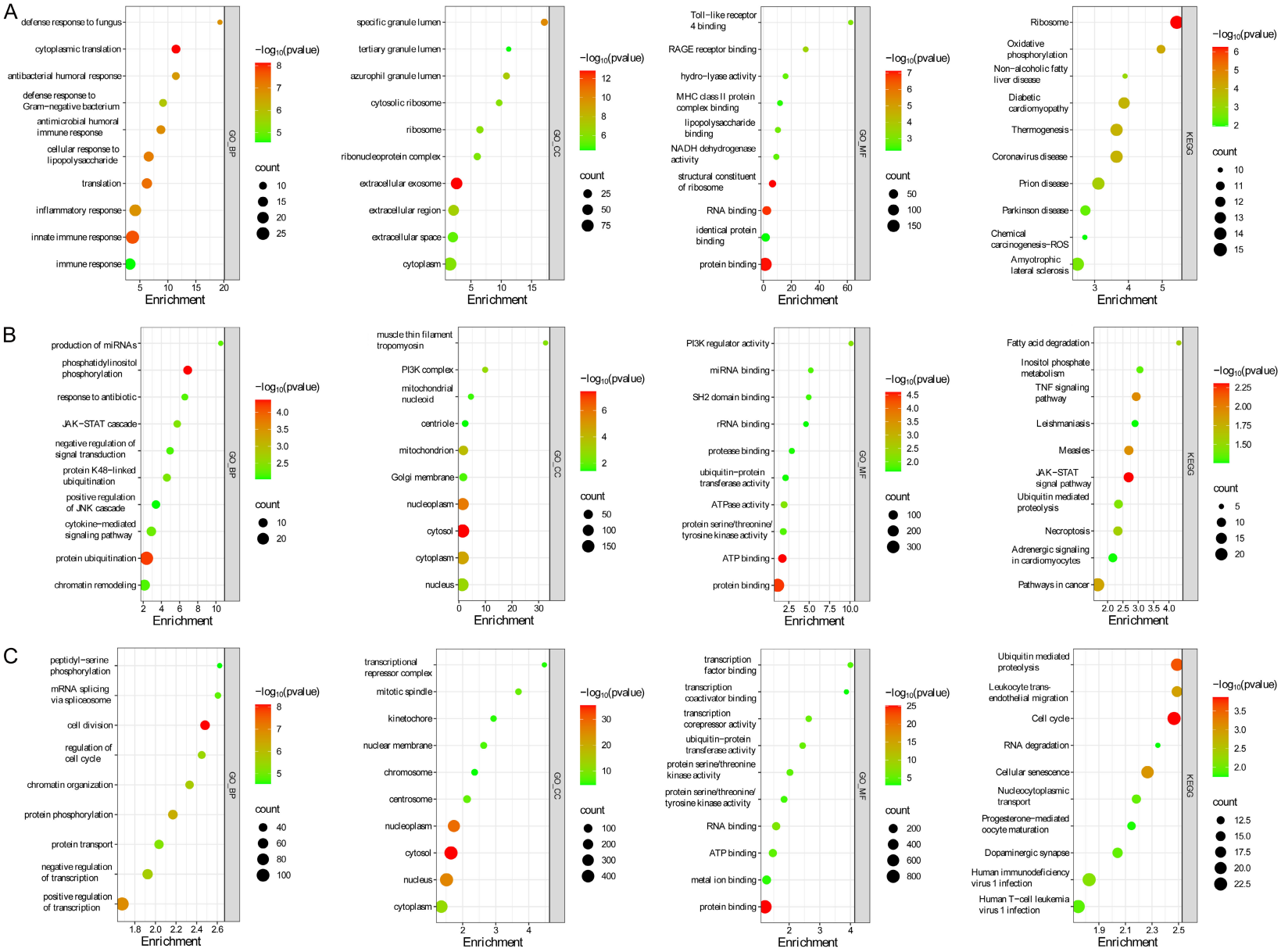

Figure 2. Function enrichment analysis of DEGs in RA datasets. A. GO and KEGG pathway analysis of DEGs in RA PBMCs. B, C. GO and KEGG pathway analysis of DEGs in RA $CD4^+$ T cells and $CD8^+$ T cells.

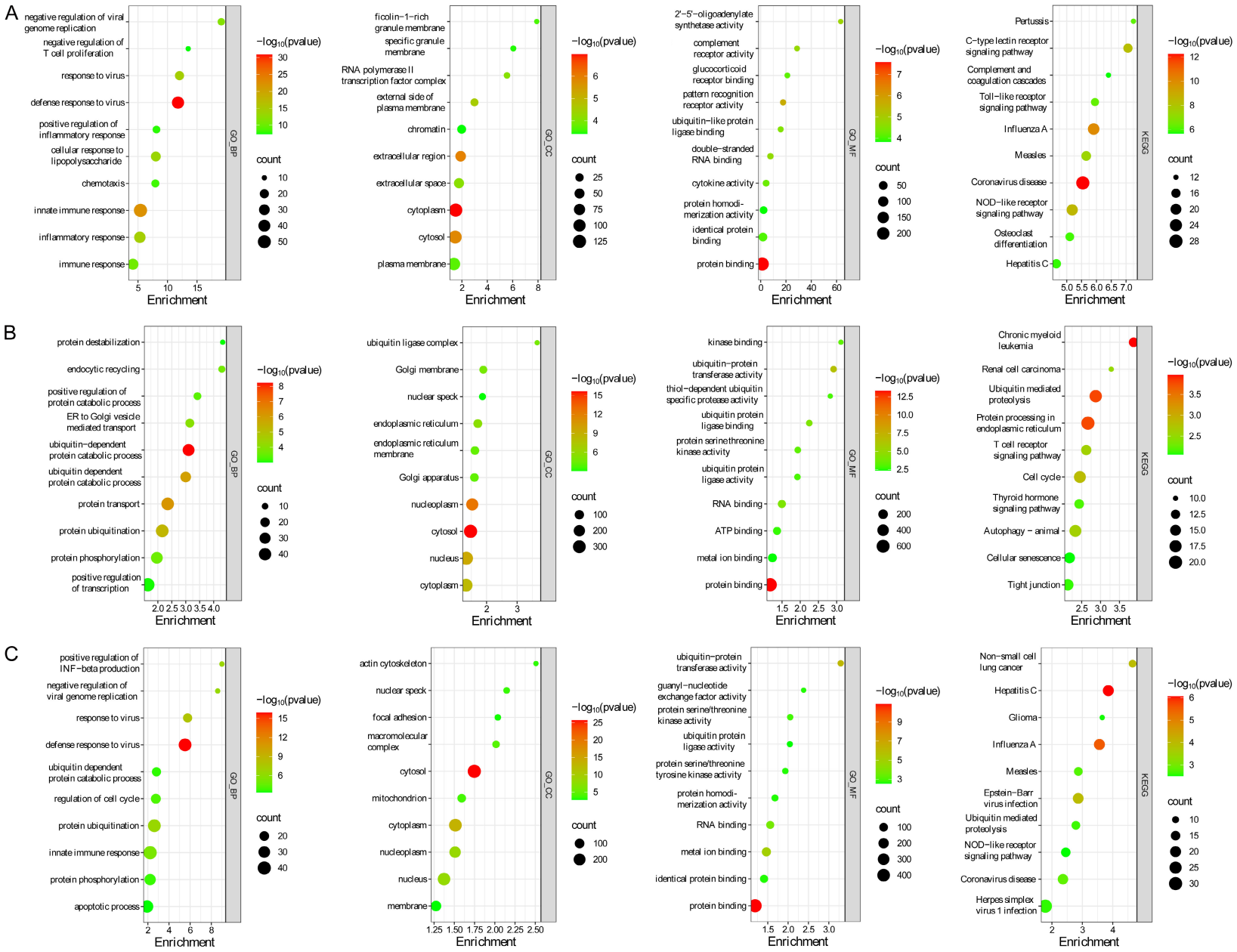

Figure 3. Function enrichment analysis of DEGs in SS datasets. A. GO and KEGG pathway analysis of DEGs in SS PBMCs. B, C. GO and KEGG pathway analysis of DEGs in SS $CD4^+$ T cells and $CD8^+$ T cells.

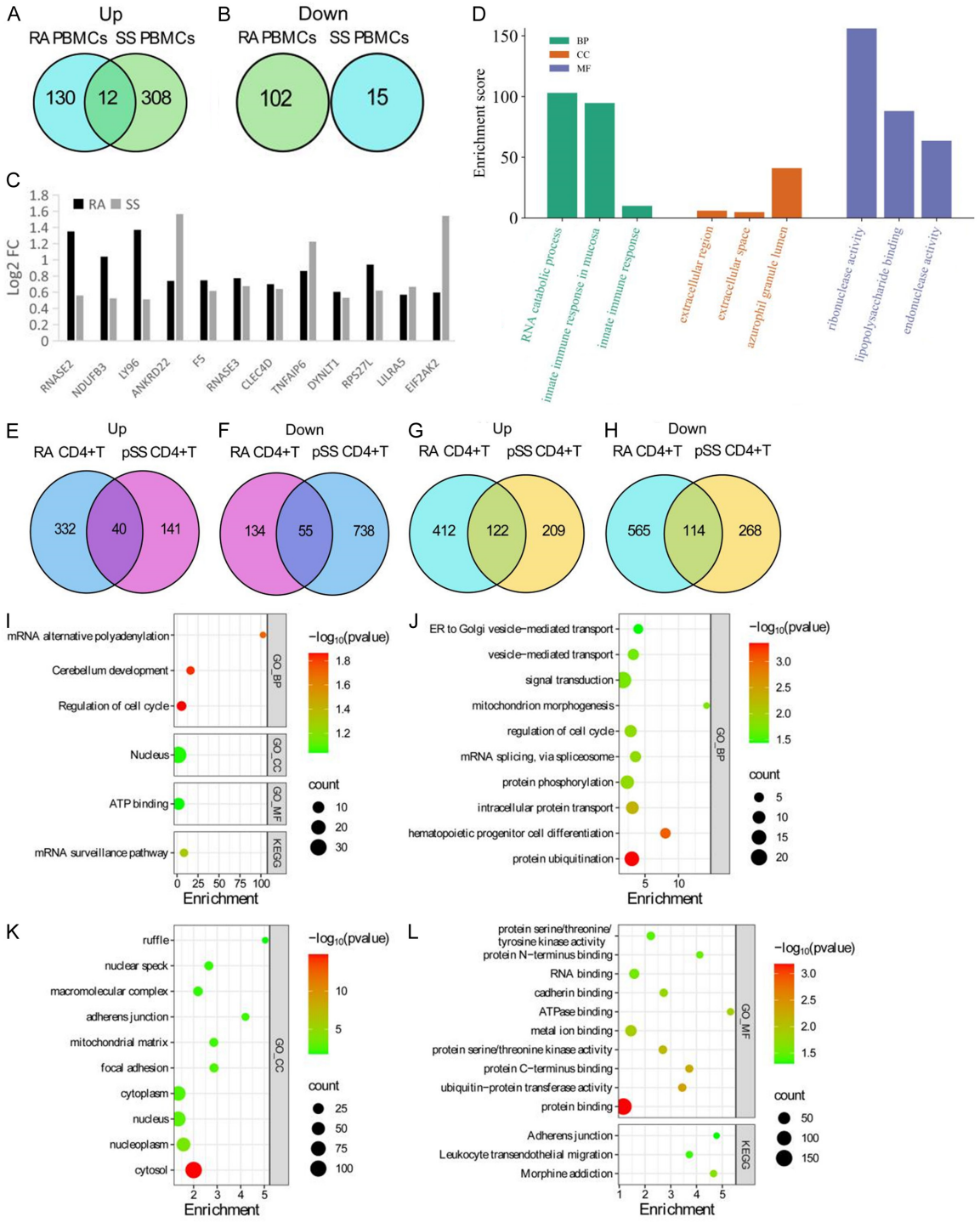

Figure 4. Screen and functional analysis of the shared DEGs in RA and SS PBMCs. A, B. Venn diagram showed the shared gene number between RA and SS PBMCs. C. The change of expression levels for the 12 shared DEGs in RA and SS PBMCs. D. Function enrichment analysis of the 12 shared DEGs. E, F. Venn diagram showed the shared DEGs number between RA and SS datasets of $CD4^+$ T cells. G, H. Venn diagram showed the shared DEGs number between RA and SS datasets of $CD8^+$ T cells. I. Function enrichment of the shared DEGs in $CD4^+$ T cells of RA and SS. J-L. Function enrichment of the shared DEGs in $CD8^+$ T cells of RA and SS.

sponse and RNA metabolic processes (**Figure 4D**).

Additionally, 95 overlapping DEGs were observed in the $CD4^+$ T cells from RA and SS data-

bases: 40 with up-regulated expression and 55 down-regulated expression, 236 overlapping DEGs were observed in the $CD8^+$ T cells, of which, 122 were up-regulated and 114 were down-regulated (**Figure 4E-H**). GO analysis showed that the DEGs in $CD4^+$ T cells were enriched to the pathways associated with cell cycle, cerebellar development, mRNA alternative polyadenylation (**Figure 4I**). While the DEGs in $CD8^+$ T cells were enriched to protein ubiquitination and phosphorylation, protein transport, cell cycle regulation, hematopoietic progenitor cell differentiation (**Figure 4J-L**).

Validation of DEGs in RA and SS patients

To validate the reliability of DEGs, the expression levels of 12 shared DEGs (RNASE2, NDUFB3, LY96, ANKRD22, F5, RNASE3, CLEC4D, TNFAIP6, DYNLT1, RPS27L, LILRA5, EIF2AK2) in PBMCs were further evaluated via the qRT-PCR in PBMC samples of RA and SS. The qRT-PCR results indicated that the expression levels of RNASE2, RNASE3, NDUFB3, and EIF2AK2 were significantly elevated in both RA and SS PBMCs. Additionally, LILRA5 expression was found to be increased specifically in SS patients. Furthermore, RPS27L showed a significant increase exclusively in RA patients (**Figure 5**).

Discussion

RA and SS are both prevalent autoimmune diseases characterized by complex clinical manifestations [21-23]. The underlying pathogenesis of RA and SS remains unclear. Furthermore, these two conditions frequently coexist in clinical practice. Therefore, identifying the shared genetic features between RA and SS is crucial for elucidating the potential mechanisms underlying RA, SS, and particularly their co-occurrence.

In our current study, we screened their common DEGs and functions in RA and SS using RNA sequencing data sets. Finally, we found 244 DEGs in RA PBMCs (142 up-regulated and 102 down-regulated) and 335 DEGs in SS PBMCs (320 up-regulated and 15 down-regulated). The RA DEGs from the PBMCs were highly enriched in cellular immune response pathways such as cellular response to lipopolysaccharide, defense response to fungi, inflammatory responses and antibacterial humoral responses. The DEGs from the SS PBMCs on the other hand were highly associated with the defense response to viruses, innate immune response, viral response and cellular reaction to lipopolysaccharide. These results emphasise the key roles of innate immunity processes in the progression of RA and SS. In addition, among these DEGs expressed in both RA and SS PBMCs, we also detected a common set of 12 up-regulated DEGs for both diseases that included the genes RNASE2, NDUFB3, LY96, ANKRD22, F5, RNASE3, CLEC4D, TNFAIP6, DYNLT1, RPS27L, LILRA5 and EIF2AK2, which were mostly associated with innate immunity response processes as well as RNA metabolic processes. We further tested the expression of the aforementioned 12 DEGs by qRT-PCR in PBMCs from RA and SS patients. The results showed upregulated levels of RNASE2, RNASE3, NDUFB3, and EIF2AK2, while the other eight genes did not change significantly in the analyzed RA or SS PBMCs. The results suggest a heterogeneity between various patients, it is therefore crucial that the DEGs detected by sequencing data need to be confirmed by clinical samples.

RNASE2 is a member of the RNase A superfamily and is one of four major secretory proteins released after eosinophil activation. It participates to anti viral activity and immunomodulatory functions in human may be a bridge between innate immunity and adaptive immunity [24]. Consistent with our study, the research conducted by Fodil M and Bovin LF. also demonstrated elevated expression levels of RNASE2 in RA. In addition, the RNASE2 expression linked to the disease is determined by some of the single nucleotide polymorphisms (SNPs), such as the rs2013109 genotype [25, 26]. However, the role of RNASE2 in RA remains unclear. The expression of RNASE2 was elevated in the PBMCs of patients with SLE, and has been associated with disease activity [27]. RNASE2 has been reported to mediate the generation of age-related B cells via the secreted interleukin-10 (IL-10) by monocytes, which is associated with SLE pathogenesis. It is necessary to figure out whether the functional mechanism of RNASE2 is similar between RA and SLE. RNASE3 also belongs to the RNase A superfamily. In our study, we found RNASE3 was overexpressed in RA and SS. It was reported that RNASE3 was overexpressed in PBMCs

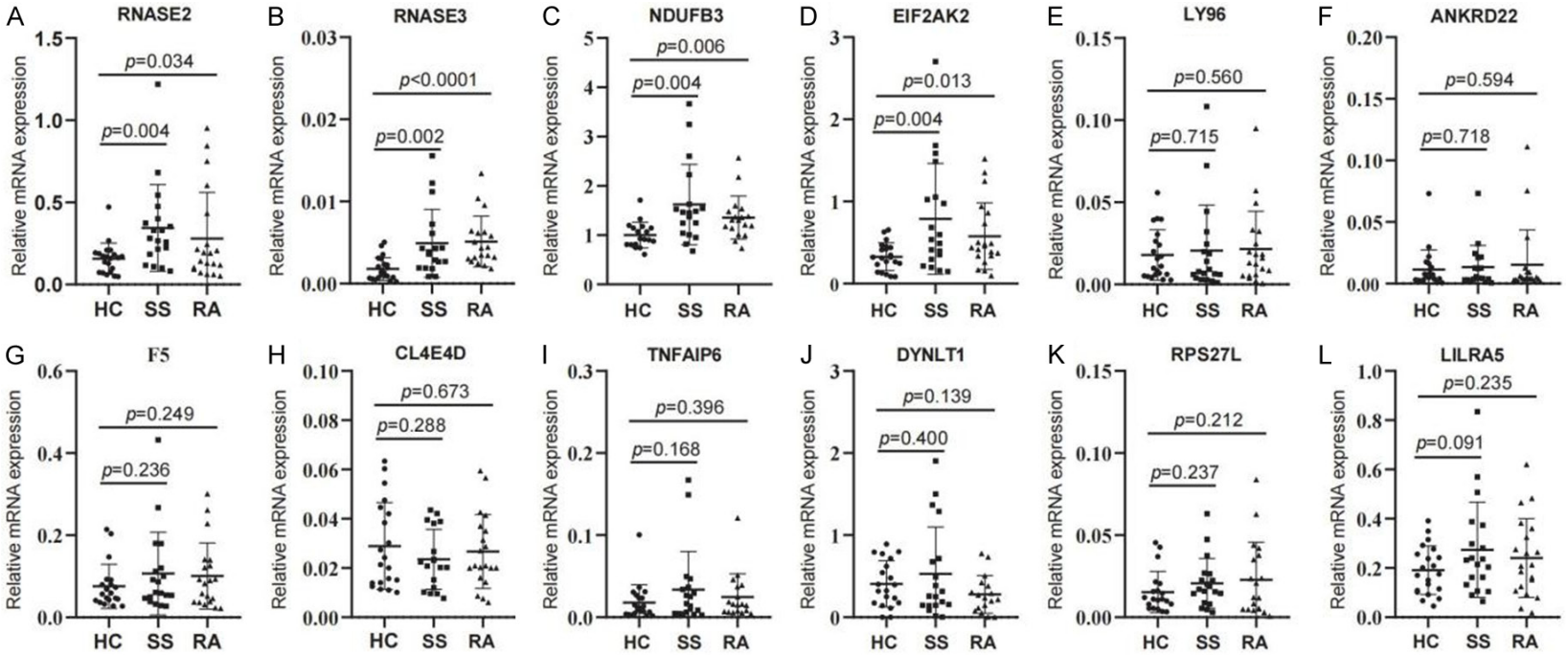

Figure 5. QRT-PCR for the 12 shared DEGs in PBMC from RA patients, SS patients and healthy controls. A-L. Comparative analysis of RNASE2, NDUFB3, LY96, ANKRD22, F5, RNASE3, CLEC4D, TNFAIP6, DYNLT1, RPS27L, LILRA5, EIF2AK2 in PBMCs.

from patients with both SLE and chronic heart failure [28]. Since cardiac failure remains a leading complication among RA patients, it is possible that RNASE3 may be a biomarker for cardiac failure in RA patients, but that has yet to be confirmed. Similarly, this study found that the level of the expression of RNASE3 can be used to predict the response to TNF-α inhibitors in the treatment of RA patients [29]. However, few papers have been published to date about the RNASE2 and RNASE3 changes and roles in SS.

NDUFB3, which is a subunit of the electron transport chain complex I, which is required for the complex I assembly, and controlling the formation of the related reactive oxygen species. With the application of single-cell RNA sequencing, previous study have indicated that NDUFB3 was up-regulated in plasma cells of RA patient [30]. In the single-cell analysis, the lactylation score was found to be remarkably high in RA patients, and core lactylation-promoting genes, including NDUFB3, were highly expressed in RA; they can be potentially biomarkers for the disease [31]. Nonetheless, the function role and clinical importance of NDUFB3 in RA and SS are still unknown. EIF2AK2 (Protein Kinase R) as a pro-viral protein and essential factor in innate immunity and functioning before activation of interferon antiviral response and acquired immunity [32]. It is demonstrated that EIF2AK2 was highly expressed in synovial tissues from RA patients than healthy controls. The author implied that it was beneficial for necroptosis of RA [33]. In SS, up-regulation of EIF2AK2 in PBMCs from SS patients and could potentially be utilized for diagnostic purposes [34]. Additionally, high EIF2AK2 expression correlates with inflammation and with the response to IFN-α and IFN-γ in SS patients [35]. Therefore, up-regulated EIF2AK2 expression in PBMCs can also be involved in the pathogenesis of RA and SS by regulating inflammatory response in patients.

However, there are some limitations in our study. First, RNASE2, RNASE3, NDUFB3 and EIF2AK2 related with RA and SS development was not investigated in the study, it is worth to conduct more in vitro and in vivo studies to verify the roles of those DEGs on the development of RA and SS. Second, because we used different population for RNA sequencing, the q-PCR validation result in our experiment might be biased and more clinical samples would be needed to verify in the future. Moreover, the prognostic role for these DEGs for the development of SS in RA patients is not so definite yet, which should be clarify in subsequent cohort studies.

Conclusions

In conclusion, our present study found significant identified DEGs and biological process in PBMCs of patients with RA and SS. In addition, through bioinformatics analysis followed by qRT-PCR validation, four shared genes-RNASE2, RNASE3, NDUFB3 and EIF2AK2 were expressed highly in RA and SS PBMCs, roles of DEGs in RA, SS and the pathogenesis of SS induced RA need to be explored in subsequent studies.

Acknowledgements

This work is supported by the Scientist Fund of Tangdu Hospital (#2021JSGJ-008 to F.L.) and The Cross Project of Air Force Medical University (#2024JC026 to F.L.).

Disclosure of conflict of interest

None.

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