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Evaluation of Genes and Molecular Pathways Common between Diffuse Large B-cell Lymphoma (DLBCL) and Systemic Lupus Erythematosus (SLE): A Systems Biology Approach

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Abstract

Background: Diffuse large B-cell lymphoma (DLBL) and systemic lupus erythematosus (SLE) are complex autoimmune disorders that present unique clinical challenges. These conditions may share underlying genetic and signaling pathways despite their distinct manifestations. Uncovering these commonalities could offer invaluable insights into disease pathogenesis, paving the way for more targeted and effective therapeutic interventions. This study embarks on a comprehensive investigation of the common genes and signaling pathways between SLE and DLBL.

Methods: The researchers scoured the Gene Expression Omnibus database, meticulously gathering microarray datasets for SLE (GSE61635) and DLBL (GSE56315). Differential expression analysis was performed, allowing the team to identify the genes that were commonly dysregulated across these 2 autoimmune conditions. To delve deeper into the biological significance of these shared genes, the researchers conducted functional enrichment analysis, network analysis, and core gene identification. Notably, the diagnostic potential of the identified hub genes was assessed using a cutting-edge neural network model.

Results: The data analysis revealed a remarkable 146 genes that were shared between SLE and DLBL, of which 111 were upregulated and 45 downregulated. Functional enrichment analysis unveiled the involvement of these shared genes in vital immune system-related processes—such as defense response to viruses, interferon signaling, and broader immune system pathways. Network analysis pinpointed 5 hub genes (IFIT3, IFIT1, DDX58, CCL2, and OASL) that emerged as central players, exhibiting a high degree of centrality and predicted to hold crucial roles in the underlying molecular mechanisms. Remarkably, the neural network model demonstrated exceptional diagnostic accuracy in distinguishing between the disease states (DLBL and SLE) based solely on the expression patterns of these hub genes.

Conclusion: The identified hub genes and their associated pathways hold immense potential as diagnostic biomarkers and may serve as valuable targets for future therapeutic explorations.

Keywords: Diffuse Large B-cell Lymphoma, Systemic Lupus Erythematous, Interferons, OASL, DDX58, CCL2, IFIT1, IFIT3

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↑What is "already known" in this topic:
Diffuse large B-cell lymphoma (DLBL) and systemic lupus erythematosus (SLE) are complex autoimmune disorders that share underlying genetic and signaling pathways despite their distinct manifestations.

→What this article adds:
This study embarks on a comprehensive investigation of the common genes and signaling pathways between SLE and DLBL. The analysis identified 146 shared dysregulated genes. Five key hub genes (IFIT3, IFIT1, DDX58, CCL2, OASL) emerged as central players.

Introduction

Recently, there have been notable advancements in genetics molecular biology, and bioinformatics to investigate the relationship between genetic factors and disease. Bioinformatics, which is the convergence of biology, information science, and computing is a vital component of biological research in the field of cancer (1, 2). We can provide pivotal insights into disease pathogenesis, identify new therapeutic targets, and pave the way for more focused and individualized treatment strategies through the integration of systems biology and bioinformatics analysis (1, 3, 4).

Systemic lupus erythematosus (SLE), a widespread autoimmune disease, is linked to a higher risk of cancers, especially lymphoma. Research indicates that this risk is 4 to 7 times greater compared with the general population (5). Diffuse large B-cell lymphoma (DLBCL) is the most prevalent form of lymphoma, representing around 40% of all cases. DLBCL tends to occur more often in men, with a male-to-female ratio of 2 to 1 (6). The underlying cause of DLBCL is unclear, although immune system disorders, such as autoimmune diseases, are known to increase the risk. The risk of lymphoma is not the same among different autoimmune diseases; its occurrence is twice as common in patients with rheumatoid arthritis (RA), 5 times in patients with systemic lupus erythematosus (SLE), and 20 times in patients with primary Sjogren's syndrome (pSS) (7). Despite the distinct clinical features and their results, recent studies have shown some common genetic and molecular features between SLE and DLBCL, indicating a possible molecular relationship between these 2 diseases (8). While DLBCL occurs more frequently in patients with SLE compared with the general population, the precise molecular mechanisms remain unclear. However, both SLE and DLBCL share overlapping genetic and signaling pathways. These common pathways could offer insights into disease pathogenesis and lead to more targeted therapeutic interventions (8, 9).

Examining the common genes and molecular pathways between these 2 diseases through a systems biology approach and bioinformatics analysis leads to facilitating the diagnostic and treatment strategies of lupus patients, who are at risk of contracting this type of lymphoma (8). This article aims to review the current state of knowledge about common genes and molecular pathways for SLE and DLBCL through a systematic review of existing studies, focusing on studies using a systems biology approach and bioinformatics analysis by collecting and analyzing the available data. This study was aimed to provide insights into common genetic markers, regulated genes, and signaling pathways involved in both diseases. In addition, the potential implications of these findings for diagnostic, prognostic, and therapeutic advances in autoimmune diseases and cancer are discussed in this article.

Methods

Microarray Data Retrieval Microarray datasets were retrieved from the Gene Expression Omnibus (GEO) database, a publicly available repository for gene expression data. Datasets for DLBCL and SLE were searched. These datasets included both case and control groups and were genotyped using a GPL platform. Ultimately, GSE56315 and GSE61635 were selected for further analysis.

GSE56315

It pertains to DLBC and consists of 88 samples, including 55 DLBC samples and 33 healthy samples. The utilized platform was the [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array (GPL570).

GSE61635

This dataset focuses on SLE and comprises 193 samples, encompassing 99 SLE samples and 30 healthy samples. Similar to GSE56315, the platform employed for this dataset is the [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array (GPL570).

Data Analysis

In our study, data analysis and the identification of shared genes were performed separately for each dataset using GEO2R online software. Differential Expression Genes (DEGs) were extracted based on predetermined criteria; the absolute value of the log fold change (|logFC|) exceeded 1 and the adjusted $P < 0.05$. Following the extraction of DEGs, a comparison was made between DLBCL and SLE DEGs using a Venn diagram to identify genes commonly dysregulated in both conditions.

Functional Enrichment Analysis of Shared Genes

A functional enrichment analysis was performed to understand the biological processes and pathways associated with the identified DEGs. In our study, DEGs were subjected to enrichment analysis using Enrichr software. To delve into the biological relevance of the DEGs, enrichment analysis was performed across 3 main categories—including biological processes (BP), cellular components (CC), and molecular functions (MF). It allowed us to uncover the diverse roles and functions of the DEGs within cellular systems. Furthermore, pathway analysis was performed using the Reactome database, a comprehensive resource for pathway analysis.

Network analysis and core gene identification network analysis and core gene identification were conducted to elucidate the key molecular interactions and identify central genes. Protein-protein interaction (PPI) analysis was performed utilizing the STRING database, with a minimum required interaction score set to 0.7. Subsequently, the generated PPI network was visualized using Cytoscape software. To further analyze the network and pinpoint the central genes, the CytoHubba plugin was employed. Importantly, genes were selected based on their degree centrality score, a measure of their importance within the network based on the number of connections they possess. In line with this analysis, the top 5 genes with the highest degree centrality scores were identified as hub genes.

Diagnostic Accuracy of the Hub Genes

The diagnostic accuracy of hub genes was evaluated us-

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ing a neural network approach implemented in Orange software, focusing on both DLBCL and SLE datasets. This neural network model was built within the orange environment; it was designed to effectively classify and differentiate between disease states based on the gene expression profiles of the identified hub genes. Stratified 5-fold cross-validation was employed to ensure robustness and reliability in the evaluation process. This approach ensures that each fold of the dataset maintains the same class distribution as the original dataset, minimizes the bias, and maximizes the generalizability of the results. Key metrics including area under the curve (AUC), classification accuracy (CA), F1 score, precision (Prec), recall, and Matthews correlation coefficient (MCC) were evaluated to gauge the performance of the neural network model.

Results

In the DLBCL dataset (GSE56315), a total of 8783 DEGs were identified, comprising 5348 upregulated and 3435 downregulated genes. Conversely, in the SLE dataset (GSE61635), 536 DEGs were detected—378 upregulated and 160 downregulated. Furthermore, upon a comparison between DLBCL and SLE datasets, 146 shared genes were identified. Among these shared genes, 111 were upregulated and 45 were downregulated across both conditions. Boxplot of each dataset is shown in Figure 1.

Furthermore, the volcano plot illustrating the distribution of DEGs has been depicted in Figure 2. These findings highlight the distinct gene expression profiles associated with DLBCL and SLE, as well as the subset of genes that exhibit dysregulation in both diseases.

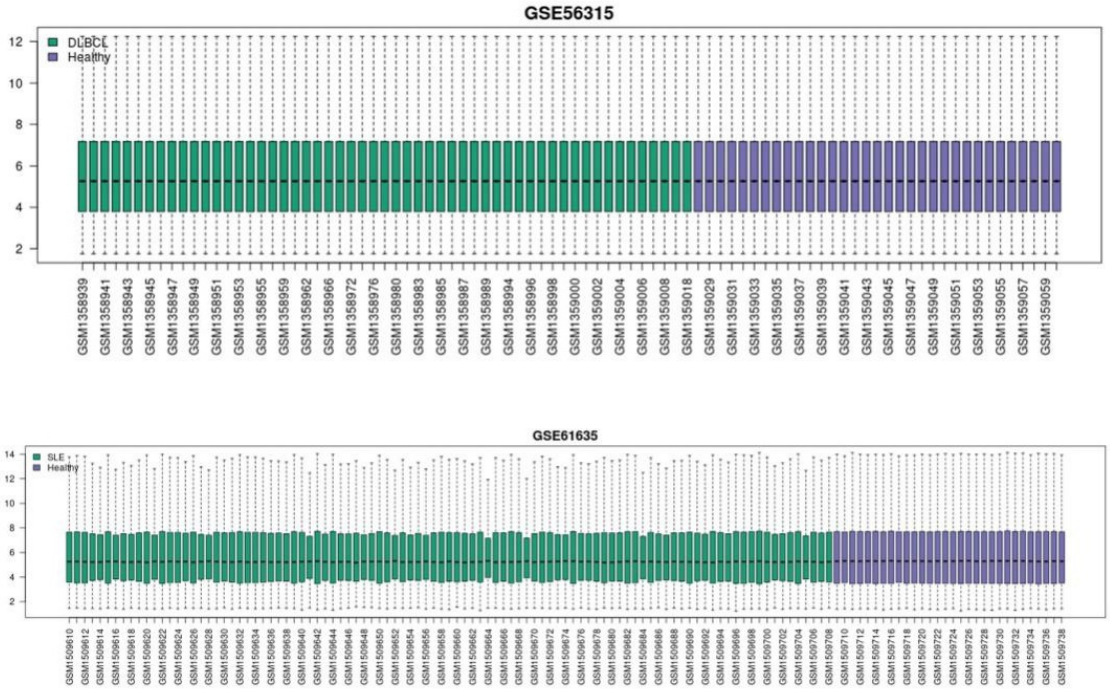

Figure 1. Boxplot of Gene Expression in DLBCL and SLE Datasets. This figure presents boxplots illustrating the distribution of gene expression levels within the DLBCL and SLE datasets. A normal distribution implies that the data is symmetrically distributed around the mean, with the majority of values clustered near the center and fewer values dispersed towards the tails of the distribution.

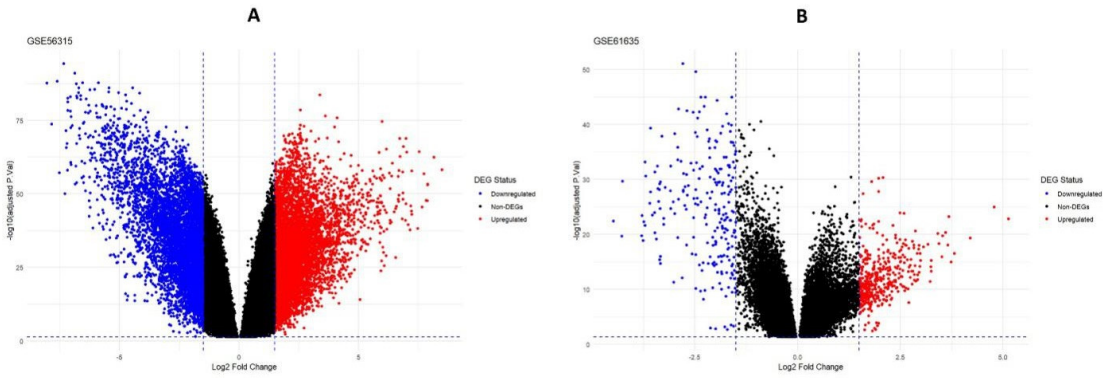

Figure 2. This volcano plot illustrates the distribution of differentially expressed genes (DEGs) in both DLBCL and SLE datasets. Each point represents a gene, with the x-axis indicating the fold change and the y-axis representing the statistical significance (e.g., -log10 p-value). Genes with significant up-regulation are depicted in red, while those with significant down-regulation are shown in blue.

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Functional Enrichment Analysis of Shared Genes

In the functional enrichment analysis of shared genes between DLBCL and SLE, significant BP, CC, MF, and pathways were identified. BP include defense response to symbiont (GO:0140546), defense response to virus (GO:0051607), and negative regulation of epithelial cell migration (GO:0010633) (Figure 3). CC encompasses the Adherens junction (GO:0005912), specific granule (GO:0042581), and early endosome (GO:0005769) (Figure 3). Molecular functions include double-stranded ribonucleic acid (RNA) binding (GO:0003725), single-stranded RNA binding (GO:0003727), and protease binding (GO:0002020) (Figure 3). Pathway Analysis (Reactome) revealed interferon-alpha/beta signaling (R-HSA-909733), interferon signaling (R-HSA-913531), and immune system (R-HSA-168256) (Figure 4). Pathway analysis indicated the importance of interferon signaling and immune system pathways in the pathogenesis of both DLBCL and SLE, suggesting potential targets for further research and therapeutic interventions. To ensure that only statistically meaningful results were considered, we applied a threshold $P < 0.05$ to identify significantly enriched terms.

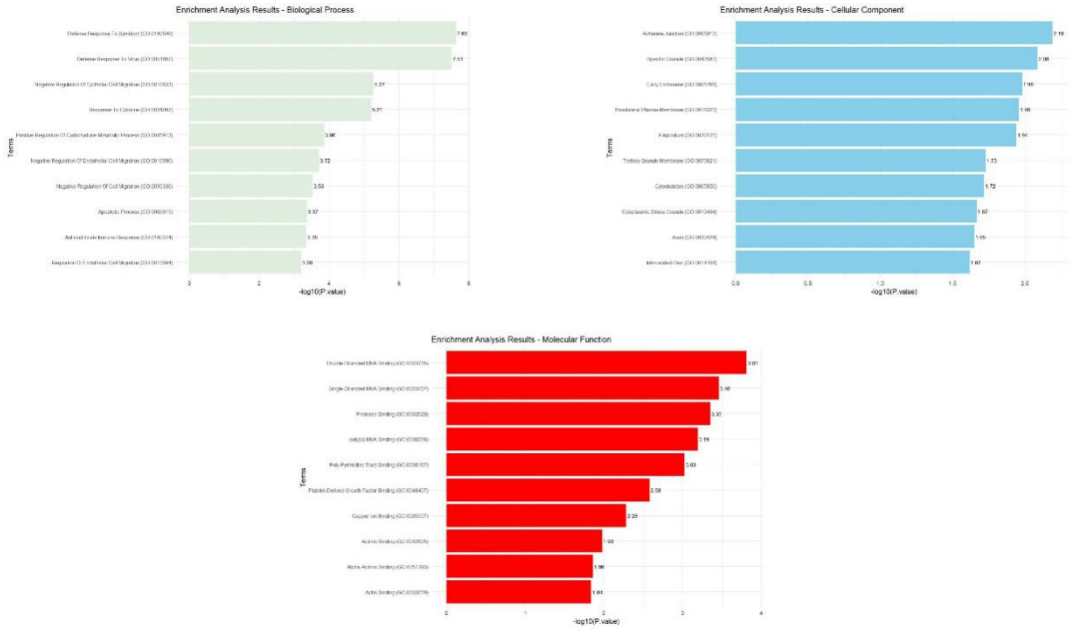

Figure 3. This figure presents the protein-protein interaction (PPI) network, visualizing the interactions among genes/proteins identified in the study. The nodes represent genes/proteins, while the edges represent the interactions between them.

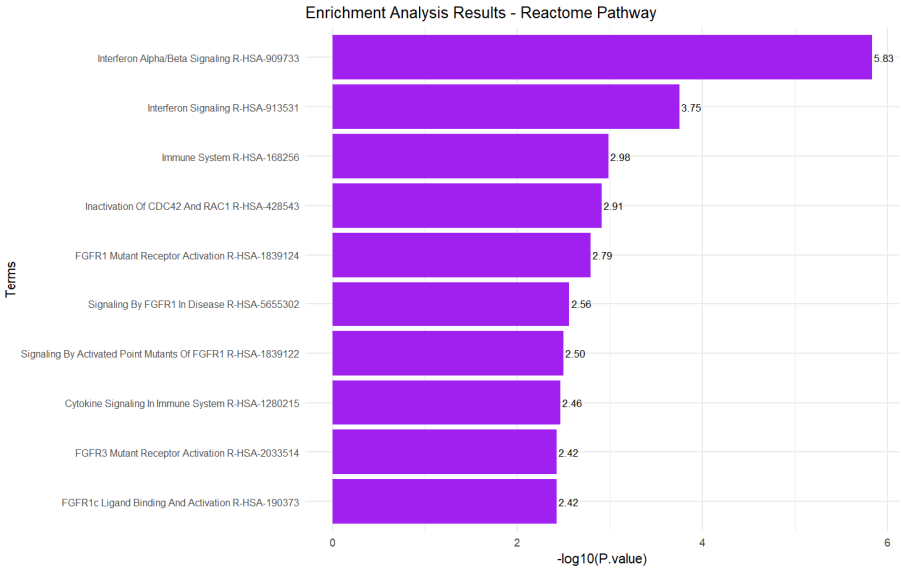

Figure 4. This figure displays enriched Gene Ontology (GO) terms associated with biological processes (BP), cellular components (CC), and molecular functions (MF) in both the DLBCL and SLE datasets. The x-axis represents the statistical significance of enrichment (-log10 p-value), while the y-axis illustrates the GO terms.

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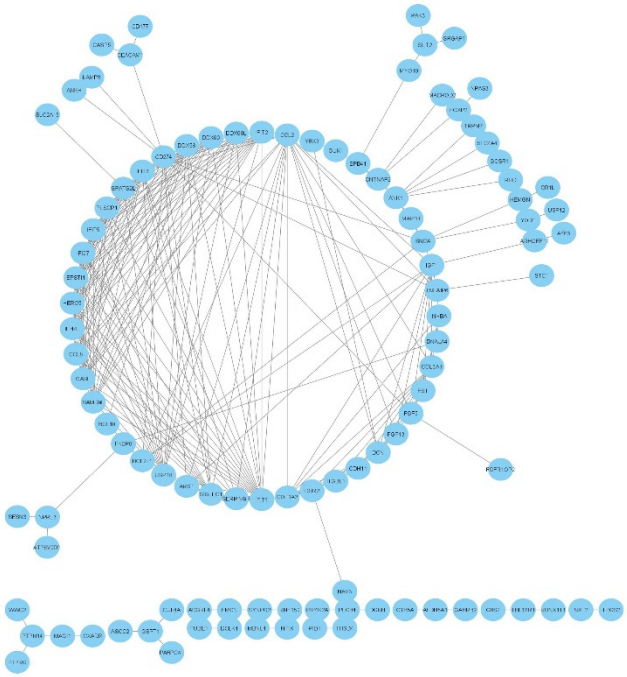

Figure 5. This figure illustrates the results of pathway analysis conducted using the Reactome database. Each point on the plot represents a Reactome pathway term, with the x-axis indicating the statistical significance of enrichment (-log10 p-value) and the y-axis representing the Reactome pathway terms.

Network Analysis and Core Gene Identification

A PPI network capturing the intricate connections among genes and proteins was meticulously constructed and visually represented (Figure 5). Then, hub genes were singled out based on their degree centrality scores unveiling the top 5 influential genes—including IFIT3, IFIT1, DDX58, CCL2, and OASL.

Diagnostic Accuracy of Hub Genes

For the diagnostic accuracy assessment of hub genes, a neural network approach was employed on both DLBCL and SLE datasets. In the DLBCL dataset, the neural network model exhibited robust performance metrics with an AUC of 0.999, classification accuracy (CA) of 0.989, F1 score of 0.989, precision of 0.989, recall of 0.989, and MCC of 0.976. Meanwhile, in the SLE dataset, the neural network model demonstrated commendable performance with an AUC of 0.995, CA of 0.953, F1 score of 0.954, precision of 0.958, recall of 0.953, and MCC of 0.8.

The results indicated that the neural network models achieved high levels of accuracy in predicting the diagnostic outcomes based on the hub genes in both DLBCL and SLE datasets.

Discussion

Several studies have shown that patients with SLE are prone to several conditions—such as cardiovascular problems (9), type 2 diabetes (10), and hematological malignancies, especially non-Hodgkin lymphomas (7). There are several risk factors for DLBCL development, such as the presence of immune deficiency syndromes (eg, HIV/AIDS) (11), environmental exposures (12, 13), and positive family history (14). Also, chronic immune dysregulation, found in autoimmune diseases—such as Sjögren syndrome, rheumatoid arthritis, and SLE—is another key risk factor in hematological malignancies (5). For instance, in patients with Sjögren syndrome developing mucosa-associated lymphoid tissue (MALT) lymphoma, the polymorphism of genes responsible for factor κB activation (ie, TNFAIP3 gene) has been found (15). Unfortunately, the exact mechanism of the higher risk of hematological malignancies such as DLBCL in SLE patients remains unclear. However, alterations in immune response, apoptosis, and cell cycle signaling pathways have been mentioned (15). This study employed a bioinformatics approach to identify shared genes and molecular pathways in SLE patients with DLBCL.

As previous studies have shown, the dysregulation of the immune system is a shared mechanism of autoimmune diseases and malignancies (7). Interferons (IFNS) are key mediators of immune responses, and it has been proven that IFN levels are elevated among patients with SLE (16). Besides immune system regulation, IFN type 1 (Interferon-α (IFN-α) and interferon-β (IFN-β)) play a role in the proliferation and survival of lymphocytes (17). IFN-α and IFN-β promote IL-2 receptor α (IL-2Rα) chain expression. IL-2 plays a role in lymphocyte proliferation by activating the JAK/STAT pathway (18). The binding of IL-2 to its receptor activates JAK tyrosine kinases, leading to the phosphorylation of the STAT transcription factors (17). The STAT complex binds to the promotor of the genes involved in cellular proliferation and tumor progression, such as pim-1 or

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c-myc genes (19). The pim-1 gene is responsible for lymphocyte proliferation and survival, and it is also a proto-oncogene in B and T-cell lymphomas (20). For instance, pim-1 encoded kinase phosphorylates CDC25A, which facilitates the progression of cells from the G1 to the S phase of the cell cycle (21).

IFN-α and IFN-β also upregulate the expression of the c-myc gene through IL-2 and JAK/STAT pathway (5). The c-myc gene plays a crucial role in cellular proliferation and is a protooncogene in different lymphomas (22). For example, c-myc proteins upregulate cyclin A2 and D2 (ie, cell cycle mediators), leading to cell cycle progression (23). Studies have shown that various microRNAs are targeted by c-myc or regulate c-myc expression (17, 23). For instance, c-myc gene products repress miR-26a in tumor cells. On the other hand, miR-33b, miR-143, and miR-145 repress the c-myc expression (23).

Other genes associated with tumorigenesis are interferon-induced proteins with tetratricopeptide repeat 1 (IFIT1) and IFIT3 (18). IFIT1 and 3 are involved in cell proliferation through the circUBAP2/miR-4756/IFIT 1/3 signaling pathway (24). CXCL1 cytokine induces the expression of a circular RNA called circUBAP2. circUBAP2 upregulates IFIT1 and 3 expression; IFIT1 and 3 upregulation leads to an increased level of IL-17 and IL-1β, responsible for cell migration and metastasis progression(24). IL-1β causes cell growth through miR-181a/PTEN axis. IL-1 β upregulates the NF-κB transcription factor, which elevates the level of miR-181a. The miR-181a inhibits the expression of the PTEN gene (ie, a critical tumor suppressor gene), leading to cell growth (19). However, miR-4756 competes with circUBAP2 for binding to IFIT 1/IFIT 3. Binding miR-4756 to IFIT1 and 3 counteracts their action, decreasing cell migration and metastasis progression (24).

Moreover, IFIT genes also affect tumorigenesis through the apoptosis pathway (25, 26). The JAK/STAT pathway regulates the IFIT genes. IFIT 1 and 2 genes are upregulated by STAT 1 and 2 transcription factors (27). IFIT1 and 2 encoded proteins bind together to form a protein complex promoting the intrinsic apoptosis pathway by activating the pro-apoptotic proteins, such as Bax or Bak, which are responsible for increasing mitochondrial permeability and activating the caspase proteins (26). However, activated IFIT3 protein binds to the IFIT1/2 protein complex, inhibits their apoptotic activity, and increases cell survival (28).

The Helicase DExD/H-box helicase 58 (DDX58) gene also has been associated with cell proliferation and growth. DDX58 encodes a protein called retinoic acid-inducible gene-I (RIG-I) (29). It has been shown that the upregulation of the DDX58/RIG-I gene inhibits cellular proliferation by inhibiting the STAT3/CSE signaling pathway (30). STAT3/CSE is a signaling pathway that promotes tumor cell proliferation, migration, and invasion (29). RIG-1 deactivates the STAT3 by hampering its phosphorylation. Activated STAT3 attaches to the promotor of the CSE gene and enhances its expression (29). The CSE gene expression inhibits apoptosis executors like caspase-3 and caspase-9, causing cell survival and proliferation (30). Also, the DDX58/RIG-1 inhibits cell proliferation through the STAT1 activation (31). The RIG-1 activates STAT1, upregulating the TRAIL-1 gene involved in cell proliferation inhibition (31). The TRAIL-1 proteins activate the caspase-8 and caspase-10, which are involved in apoptosis progression (32). DDX58 has been recognized as an immune response factor and is the mediator of IFN antiviral responses. Recent studies have shown that RIG-1 is activated by viral RNA (33). Activated RIG-1 recruits a group of molecules to activate a kinase complex (TANK binding kinase 1 - IκB kinase) (34). This kinase complex activates factors such as IRF3 and IRF7, which upregulate the expression of type 1 IFN and cytokines, leading to tumor proliferation inhibition (34). Recent studies have shown that lenalidomide drug, which is an effective drug choice for DLBCL, acts by activating RIG-1 domains and slows the proliferation of the tumor cells (35).

The role of the chemokine ligand 2 (CCL2) in cell proliferation and cancer has also been mentioned in the literature (33). CCL2 is a chemokine ligand that binds to its receptor called CCR2. The CCL2-CCR2 pathway enhances tumor cell survival by stimulating the PI3K/AKT signaling pathway. CCL2-CCR2 activates the PI3K kinase, leading to the phosphorylation and activation of AKT (protein kinase B) (33). AKT kinase activates the mTOR protein complex 1 (mTORC1) (34), which is a protein complex that activates multiple downstream pathways associated with apoptosis inhibition and tumor survival (35). mTORC1 upregulates the expression of an apoptosis inhibitor called survivin (34). Survivin hampers the activation of caspase 9—an essential protein in apoptosis progression (35). mTORC1 also inhibits apoptosis by downregulating the GSK-9 kinase (30). Downregulated GSK-9 inhibits caspase 3, leading to apoptosis inhibition (30). Epigenetic mutations, such as histone acetylation, have also been linked to tumor progression in DLBCL (33). Previous studies have shown that knockdown of the genes responsible for histone acetylation of the CCL2 gene (eg, CREBBP or EP300), leads to the activation of the CCL2 expression (33). CCL2 chemokine recruits tumor-associated macrophages to the tumor site (33). These macrophages create an immunosuppressive microenvironment that facilitates tumor progression and proliferation (33).

Also, the CCL2-CCR2 axis positively causes tumor survival by mediating tumor angiogenesis (27). CCL2 ligand facilitates tumor angiogenesis by stimulating endothelial cells to release several angiogenetic factors through the MAPK/ERK signaling pathway (31). The CCL2, which phosphorylates ERK1 and 2, activates MAPK kinase (32). Phosphorylated ERK1 activates transcription factor Ets-1. Ets-1 subsequently upregulates the expression of several angiogenetic factors, such as the VEGF receptor, angiopoietin receptor, and integrins 3 subunits (31).

Also, it is proved that 2'-5' oligoadenylate synthetase-like (OASL) expression is associated with increased cell proliferation, migration, and malignant transformation (36). IFNs upregulate the expression of OASL through the JAK/STAT signaling pathway (36, 37). The STAT1 transcription factor is activated upon IFN- β stimulation and upregulates the OASL gene. OASL protein also activates

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the mTOR protein complex 1 (mTORC1) signaling pathway leading to cell proliferation and cancer formation (36). mTORC1 plays a role in cancer progression in multiple ways (30). For instance, mTORC1 inhibits the activity of ring finger protein 168, a protein responsible for histone ubiquitination (30). This leads to decreased histone ubiquitination after deoxyribonucleic acid (DNA) damage, leading to reduced genome stability after DNA damage, which predisposes the genome to malignant transformation and cancer (30).

The mTORC1 also promotes tumor metastasis and invasion through activating matrix metalloproteinase (38). Metastasis and invasion rely on proteolytic enzymes such as matrix metalloproteinase (MMP) (especially MMP-2 and MMP-9) to degrade the extracellular matrix and basement membrane (38). mTOR upregulates the MMP-2 and 9, facilitating invasion and metastasis (38).

Unfortunately, this study had some limitations. First, all data utilized in this study were sourced from public datasets that provided limited clinical information. Second, no in vitro experiments have been done to corroborate these results and investigate the role of these shared genes in SLE and DLBCL. Third, datasets did not include detailed individual characteristics such as disease stage, specific medications, chemotherapy regimens, demographics, or other clinical variables. These genes can be investigated as potential biomarkers and therapeutic options, and we hope that this paper, as a theoretical guide, could pave the way for further research.

Conclusion

This study investigated the possible shared genes between SLE and DLBCL (IFIT3, IFIT1, DDX58, CCL2, and OASL) and demonstrated the possible molecular pathways of these 2 conditions. We found that altered expression of these genes leads to the dysregulation of the immune system and its mediators (eg, IFNs, cytokines), which are crucial factors for both SLE and DCLBL pathogenesis. The abnormal expression of these genes also causes alterations in the cell cycle, apoptosis, and angiogenesis pathways, which are critical signaling pathways in both. We hope this theoretical study guides future in vitro research to validate these data and clarify the shared pathways of these 2 conditions.

Authors' Contributions

The study was conceptualized and designed by B.SH, A.H, and R.M. Data analysis was performed by R.M. The manuscript was written and prepared by B.SH, A.GH, S.P., A.H. and L.H.

Ethical Considerations

Not Applicable.

Acknowledgment

Not applicable.

Conflict of Interests

The authors declare that they have no competing interests.

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