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Uncovering molecular mechanisms and therapeutic targets in systemic lupus erythematosus through integrative transcriptomic and network-based analysis

Mozhdeh Ghamari[1], Arman Hosseini[2], Forouzan Amerizadeh[3,4*]

[1]Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Cancer Molecular Pathology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

***Correspondence to**
Forouzan Amerizadeh, Email: amerizadehf4011@mums.ac.ir, amerizadehf951@gmail.com

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disorder with heterogeneous clinical manifestations and limited specific biomarkers. Advances in transcriptomic profiling offer an opportunity to dissect underlying molecular mechanisms and identify therapeutic targets.

Objectives: To perform a comprehensive bioinformatics analysis of gene expression profiles in peripheral blood of SLE patients and to identify differentially expressed genes (DEGs), functional pathways, key regulatory genes (hub genes), and druggable targets.

Materials and Methods: This is an *in-silico* study based on gene expression data (GSE17755) from 10 SLE patients and 20 healthy controls were analyzed using GEO2R. DEGs were subjected to functional enrichment analysis [Gene ontology (GO) and Reactome], protein-protein interaction (PPI) network construction (STRING, Cytoscape), hub gene identification (CytoHubba), cluster detection (ClusterONE), and drug-target interaction mapping (DrugBank).

Results: A total of 1,450 DEGs were identified between SLE patients and healthy controls. Gene ontology and Reactome analyses highlighted enrichment in innate immune responses, interferon signaling, and cytokine-mediated pathways. Thirteen key hub genes including GAPDH, PTEN, PTPRC, UBA52, and ISG15 were identified across multiple centrality metrics. ClusterONE detected significant modules enriched in immune-related genes, ribosomal proteins, keratin family genes, and transcription factors. Drug-target analysis revealed GAPDH as the most connected node, interacting with compounds like artenimol, omigapil, and xanthinol, indicating potential avenues for drug repurposing.

Conclusion: Our integrative analysis highlighted interferon signaling, cytokine-mediated pathways, and innate immune responses as central mechanisms in SLE. Drug–target mapping suggested several compounds, including artenimol, omigapil, NADH, 4-(2-aminoethyl) benzenesulfonyl fluoride, xanthinol, copper, and phosphatidylethanolamine, as potential modulators of key hub genes. These findings provide preliminary hypotheses that may guide future research; however, additional validation in molecular (*in-vitro*) experiments and animal (*in-vivo*) models is required before any translational application can be considered.

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Introduction

Systemic lupus erythematosus (SLE) is a persistent autoimmune condition involving systemic inflammation, in which immune tolerance is disrupted, leading to the generation of autoantibodies targeting intracellular components. This immune dysregulation results in the accumulation of antigen–antibody complexes, activation of the complement cascade, and subsequent widespread damage to various tissues and organs (1). Systemic lupus erythematosus affects multiple systems including the skin, joints, kidneys, cardiovascular system, and central nervous system, with a highly variable clinical presentation (2). Although notable progress has been made in elucidating the mechanisms of autoimmunity and improving immunosuppressive treatment options, SLE continues to pose considerable difficulties in both diagnosis and management. These challenges arise from its clinical heterogeneity, the episodic nature of disease activity, and the current absence of reliable biomarkers for monitoring or predicting disease progression (3).

The underlying molecular mechanisms that drive the initiation and progression of SLE are complex and multifactorial, involving genetic predisposition, epigenetic modifications, environmental triggers, and dysregulated immune signaling (4). Traditional diagnostic

Key point

- Transcriptomic profiling of peripheral blood identified 1,450 DEGs in systemic lupus erythematosus (SLE) patients.
- Enrichment analysis revealed activation of interferon signaling and immune response pathways.
- Hub genes including GAPDH, PTEN, and UBA52 were central in the PPI network.
- ClusterONE uncovered functional gene modules linked to innate immunity, ribosomal activity, and epithelial structure.
- Drug-target mapping suggests GAPDH as a promising candidate for drug repurposing in SLE therapy.

markers such as anti-dsDNA and complement levels are often insufficient to fully reflect disease activity or guide therapeutic decisions (5). In recent years, high-throughput transcriptomic profiling has emerged as a powerful tool to investigate gene expression changes in SLE patients, providing insights into immune system dysregulation, type I interferon signatures, and potential pathogenic pathways (6). Peripheral blood, in particular, serves as a practical and informative sample source, reflecting systemic immune responses and enabling the identification of differentially expressed genes (DEGs) associated with disease states (7).

Integrative bioinformatics approaches allow for a comprehensive interpretation of transcriptomic data. Gene ontology (GO) and Reactome-based enrichment analyses are widely conducted to uncover critical biological pathways, cellular roles, and molecular activities linked to the expression profiles of DEGs (8). Building protein-protein interaction (PPI) networks provides insight into the relational architecture of the genes, allowing detection of hub nodes that may serve essential regulatory functions based on their topological prominence (9). Additionally, clustering algorithms such as ClusterONE can uncover functional gene modules, or sub-networks, that may represent biologically coherent units involved in specific disease-related pathways (10). Moreover, the integration of drug-target interaction data with transcriptomic findings holds promise for translational applications (11). By identifying existing compounds that target hub proteins, researchers can explore opportunities for drug repurposing or novel therapeutic development, particularly valuable in complex autoimmune diseases like SLE, where treatment options remain limited and often nonspecific (12).

Objectives

In the present study, we conducted a comprehensive transcriptomic and network-based analysis of peripheral blood samples from SLE patients using publicly available microarray data. After identifying DEGs, we constructed a PPI by STRING and visualized it using Cytoscape. We then performed functional enrichment analysis and Reactome databases, identified hub genes through topological algorithms implemented in CytoHubba, and detected significant gene clusters using ClusterONE. Finally, we assessed the therapeutic potential of hub genes through drug-target interaction analysis using curated pharmacological databases. This integrative approach provides novel insights into the molecular architecture of SLE and identifies candidate biomarkers and druggable targets that may contribute to future diagnostic and therapeutic strategies.

Materials and Methods

Data acquisition and preprocessing

In the present *in-silico* study, publicly available gene expression profiles were retrieved from the NCBI GEO repository (accession ID: GSE17755). This dataset includes gene expression profiles derived from peripheral blood samples of 10 patients with SLE and 20 healthy controls, analyzed using the Hitachisoft AceGene Human Oligo Chip 30K 1 Chip Version (platform ID; GPL1291). Differential expression analysis was conducted using GEO2R, an interactive online tool that applies the limma (Linear Models for Microarray Data) package to identify DEGs. In our study, Log2 transformation was auto-detected, and the NCBI-generated platform annotation was conducted for mapping probe identifiers. Moreover, genes were considered significantly differentially expressed if they had an adjusted P value < 0.05 (based on the Benjamini–Hochberg false discovery rate [FDR] correction) and a log2 fold change threshold greater than ±0.37, corresponding to a fold change of approximately ≥1.29 or ≤0.77 (13).

Gene ontology and biological pathway enrichment analysis

The resulting list of DEGs was submitted to the STRING database (version 11.5) to construct the protein network. Interactions with a confidence score above 0.4 were included (14). The STRING-generated network was exported and further analyzed in Cytoscape (version 3.9.1) for topological exploration and functional enrichment (15).

Functional annotation of the DEGs network was performed using the BiNGO plugin in Cytoscape. GO categories including biological process (BP), cellular component (CC), and molecular function (MF) were assessed. Overrepresented GO terms were identified using the hypergeometric test, and a Benjamini–Hochberg FDR correction was applied. GO terms with an adjusted p-value below 0.01 were reported as statistically significant (16).

For pathway enrichment analysis, DEGs were mapped to curated pathways in the Reactome database via the STRING interface. Pathways with enrichment FDR < 0.05 were retained to identify potential molecular mechanisms and biological cascades involved in the studied condition (17).

Identification of hub genes in the PPI network

The protein-protein interaction network constructed via the STRING database was imported into Cytoscape (version 3.9.1) for topological analysis. To identify

central genes with high connectivity, the network was analyzed using the CytoHubba plugin. Four topological algorithms—maximal clique centrality (MCC), maximum neighborhood component (MNC), density of maximum neighborhood component (DMNC), and degree—were applied to rank the nodes based on their centrality scores. The top five genes with the highest scores across these algorithms were selected as hub genes, representing key regulatory proteins potentially involved in the underlying biological processes of the studied condition (18).

Cluster analysis of the PPI network

Following the construction of PPI network using STRING and its visualization in Cytoscape (version 3.9.1), clustering analysis was performed to identify functionally significant gene modules. The Cytoscape app, CytoCluster, was employed, and the ClusterONE (clustering with overlapping neighborhood expansion) algorithm was applied to detect densely connected regions within the network. ClusterONE identifies overlapping clusters based on cohesiveness and topological density, making it suitable for biological networks with shared components. All statistically significant clusters (with *P* values<0.05) were selected and visualized. Each cluster represents a group of genes with potentially shared biological functions or involvement in the same molecular complexes (19).

Drug-target interaction analysis

The identified hub proteins were subjected to drug-target interaction analysis to explore their potential as therapeutic targets. Each hub gene was queried against the DrugBank database to identify known compounds and bioactive molecules that interact with these proteins. The analysis was conducted using gene or protein identifiers, and all retrieved drug interactions were manually reviewed to confirm their relevance. Compounds targeting one or more of the hub proteins were compiled, providing a preliminary insight into the drug ability of key molecular regulators implicated in the disease context (20).

Results

Differential expression analysis

To identify DEGs between SLE patients and healthy controls, we performed expression analysis on dataset GSE17755. A total of 30 peripheral blood samples, including 10 from SLE patients and 20 from healthy individuals were analyzed. The distribution of gene expression values across all samples was first assessed using expression density plots (Figure 1A). The density curves for case and control groups exhibited similar overall shapes and ranges, suggesting appropriate normalization and comparability of expression intensity values between the two groups.

Differential expression analysis revealed a distinct set of upregulated and downregulated genes. The volcano plot (Figure 1B) illustrates the relationship between statistical significance (–log10 adjusted *P* value) and magnitude of change (log2 fold change). Genes with an adjusted *P* value < 0.05 were considered significant and are highlighted in red (upregulated) and blue (downregulated). A total of 1450 dysregulated genes were identified indicating substantial transcriptional alterations in SLE samples compared to controls. The MA plot (Figure 1C) further depicts the log2 fold change (y-axis) versus average log2 expression values (x-axis). The spread of significant DEGs (colored points) above and below the zero fold change line reflects consistent dysregulation across a range of expression levels. These findings indicate that peripheral blood from SLE patients displays a robust and distinct transcriptional signature, with statistically significant alterations in gene expression that may underlie key immunopathological mechanisms in the disease.

Integrated Reactome and GO analysis uncovers key functional and subcellular profiles of DEGs

Pathway and GO enrichment analyses were conducted to identify the functional characteristics of the DEGs. Among the enriched Reactome pathways, the most prominent were innate immune system, interferon

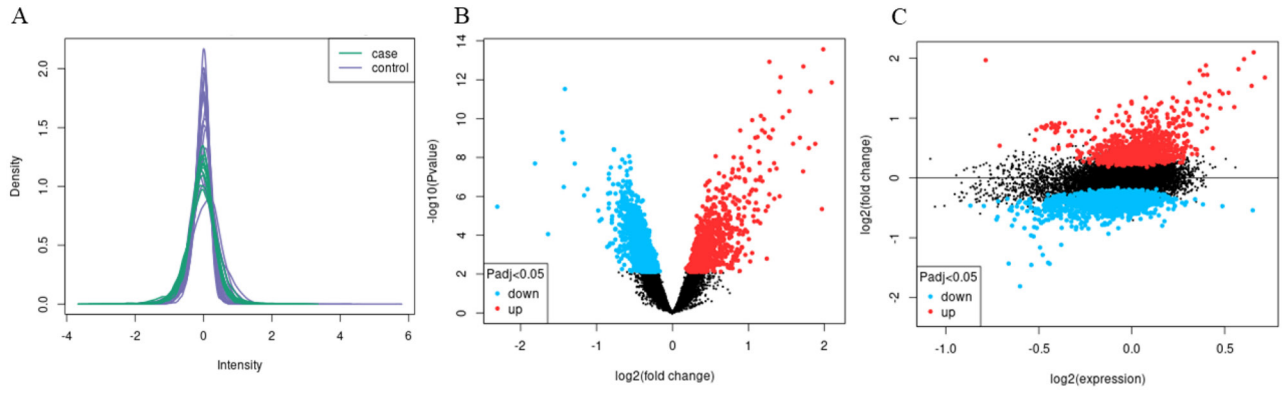


Figure 1. Visualization of differential gene expression analysis results between SLE patients and healthy controls. (A) Density plot of normalized expression values indicating comparable distribution between case and control groups. (B) Volcano plot showing significantly upregulated (red) and downregulated (blue) genes (adjusted *P* value < 0.05). (C) MA plot displaying log2 fold change versus average expression, highlighting DEGs.

signaling, immune system, signal transduction, and cytokine signaling in the immune system, highlighting a strong involvement of DEGs in immunological and signaling responses. In the biological process category, enrichment results revealed major functional processes including cellular process, signaling, signal transmission, biological regulation, and response to stimulus. These terms emphasize the active role of the DEGs in modulating intracellular signaling networks and regulatory pathways associated with environmental stimuli and cellular behavior. For the cellular component ontology, the DEGs were predominantly localized to compartments such as the cytoplasm, intracellular organelle, organelle part, cytosol, and endoplasmic reticulum. This distribution suggests that the functional activity of these genes occurs within key intracellular environments linked to protein synthesis, modification, and trafficking. Finally, in the molecular function category, two dominant terms were observed; protein binding and binding. These functions indicate that the DEGs largely participate in molecular interactions, particularly protein–protein associations critical to signaling and structural stability. Together, these results provide a focused overview of the biological roles, molecular functions, and cellular localizations of DEGs, grounded in the visual evidence provided (Figure 2).

Identification of hub genes

To identify the most influential nodes in the PPI network, topological analysis was performed using CytoHubba in Cytoscape. Four centrality algorithms—MCC, MNC, DMNC, and Degree, were employed to rank genes based on their importance in network topology. The top-ranked genes from each algorithm were selected as hub genes and are presented in Figure 3 and Table 1. Using the MNC/Degree criteria, the top genes identified were GAPDH, UBA52, PTEN, and PTPRC, with H4C6 additionally ranked by Degree alone. The DMNC algorithm highlighted IFRD1, HERC5, IFITM2, and MX2 as central nodes, while the MCC algorithm identified IFI35, ISG15, OASL, and IFIT3 as the top-scoring hub proteins. These hub genes are potentially critical regulators in the biological system under study, reflecting key positions in network connectivity and functional relevance.

Identification of functional gene clusters through network-based clustering

To uncover densely interconnected gene modules within the PPI network, a clustering analysis was performed using the ClusterONE algorithm. The analysis revealed several statistically significant clusters that varied in size, density, and biological context.

The two largest clusters, consisting of 36 and 33 nodes respectively, exhibited high internal connectivity with densities of 0.614 and 0.606, and P values of 1.71×10^{-5} and 0.003. These clusters likely represent major functional cores in the network. The first cluster was enriched with interferon-stimulated and immune-related genes such as IFI35, IFIT3, MX2, OAS1, and SP100, indicating a central

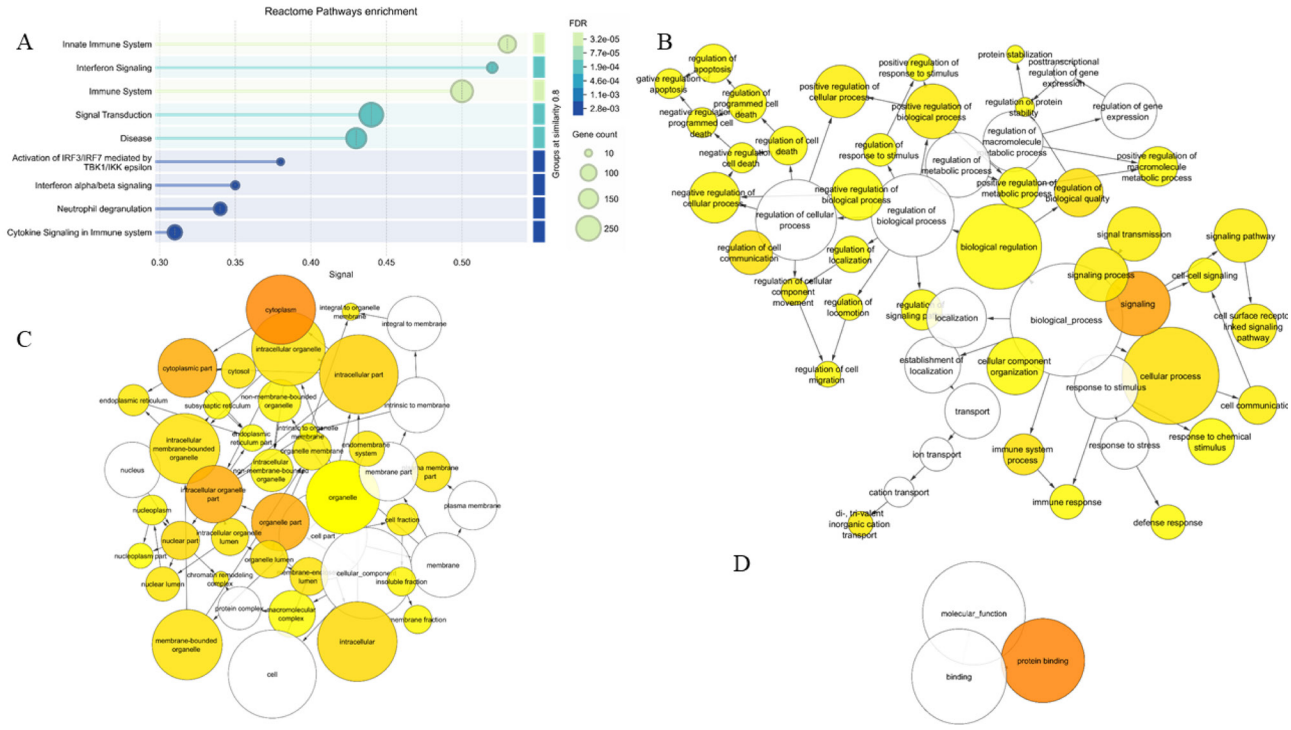


Figure 2. Functional enrichment analysis of differentially expressed genes. (A) Reactome pathway enrichment analysis of DEGs. Pathways are ranked by gene ratio and statistical significance. (B) Gene ontology) biological process) enrichment network visualized using BiNGO. (C) (cellular component) enrichment map showing that DEGs are primarily localized to intracellular structures. (D) Gene ontology (molecular function) of network.

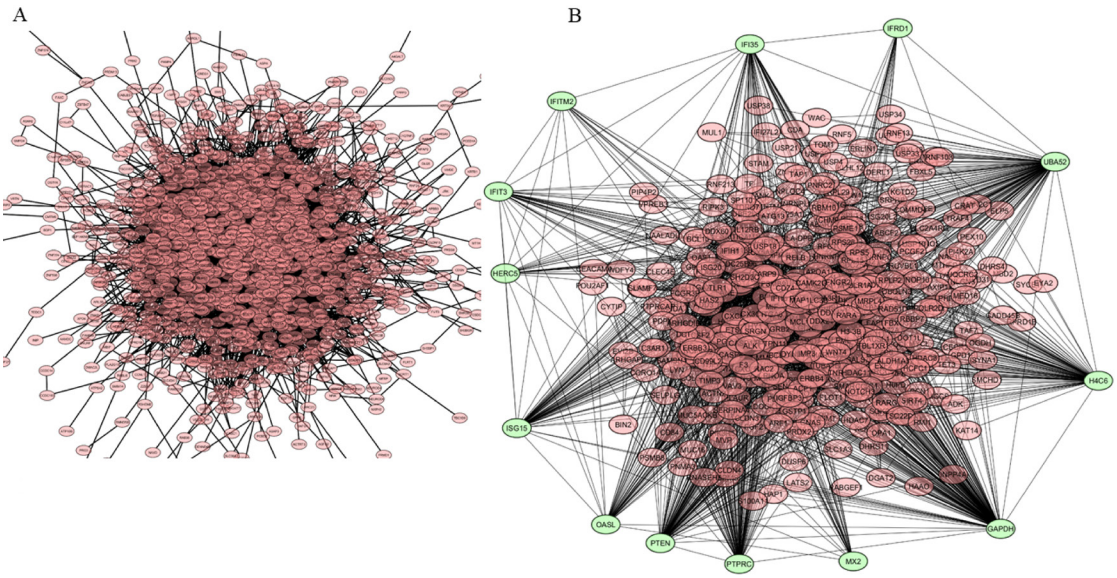


Figure 3. Identification of hub genes in the PPI network using four topological algorithms. (A) All dysregulated proteins. (B) Hub genes were identified based on four centrality measures applied by the CytoHubba plugin in Cytoscape.

role in innate immune signaling. The second cluster included a large number of ribosomal proteins such as RPL13, RPLP1, RPS14, and RPL3, suggesting involvement in translation and ribosome biogenesis.

In addition to the large clusters, several smaller but statistically significant modules were also detected. One cluster composed of KRT23, KRT24, KRT34, and KRT81 represented a tightly connected keratin gene family module ($P = 0.026$), potentially associated with epithelial structure or differentiation. Another notable cluster included transcription-related zinc finger proteins such as ZSCAN2, ZNF496, ZNF397, and ZKSCAN9, observed in multiple overlapping modules with p-values ranging from 0.026 to 0.048. Further, a distinct module comprising NAP1L2, MAGEB2, and FTHL17 emerged as a compact cluster with high quality (1.0) and P value of 0.030, indicating a strong co-regulatory potential. Finally, a highly dense cluster (density = 1.0) containing neuronal acetylcholine receptor subunits CHRNA6, CHRNB2, and CHRNB3 was detected, suggesting a role in synaptic signaling or neural communication. Altogether, the clustering analysis identified both broad regulatory hubs and specific functional units, each potentially contributing to distinct aspects of the biological processes underlying the condition of interest (Figure 4).

Table 1. Identification of top hub proteins based on multiple centrality algorithms in the PPI network

Rank	Protein	Algorithm
1,1	GAPDH	MNC/Degree
2,2	UBA52	MNC/Degree
3,3	PTEN	MNC/Degree
4	PTPRC	MNC
1	IFI35	MCC
2	ISG15	MCC
3	OASL	MCC
4	IFIT3	MCC
1	IFRD1	DMNC
2	HERC5	DMNC
3	IFITM2	DMNC
4	MX2	DMNC
4	H4C6	Degree

MNC: Maximum neighborhood component, MCC: Maximal clique centrality, DMNC: Density of maximum neighborhood component, Degree: Degree centrality.

Drug-target interaction analysis

To explore the therapeutic relevance of the identified hub proteins, a drug-target interaction analysis was performed. Among the hub genes, GAPDH was found to interact with the highest number of compounds. A total of nine drugs or bioactive molecules were identified as potential GAPDH binders, including 4-(2-aminoethyl) benzene sulfonyl fluoride, adenosine-5-diphosphoribose, artenimol, copper, NADH, omigapil, thionicotinamide-adenine-dinucleotide, xanthinol, and phosphatidylethanolamine. These drugs span various categories such as experimental, approved, investigational, withdrawn, and nutraceutical agents. However, the pharmacological action for most of them remains classified as unknown, indicating a need for further experimental validation. In addition, PTEN, another key hub protein, was identified as a target for Phosphatidylethanolamine, suggesting possible implications for targeting PTEN-regulated pathways. Overall, this analysis highlights several druggable interactions involving central hub proteins, particularly GAPDH, and provides a preliminary foundation for

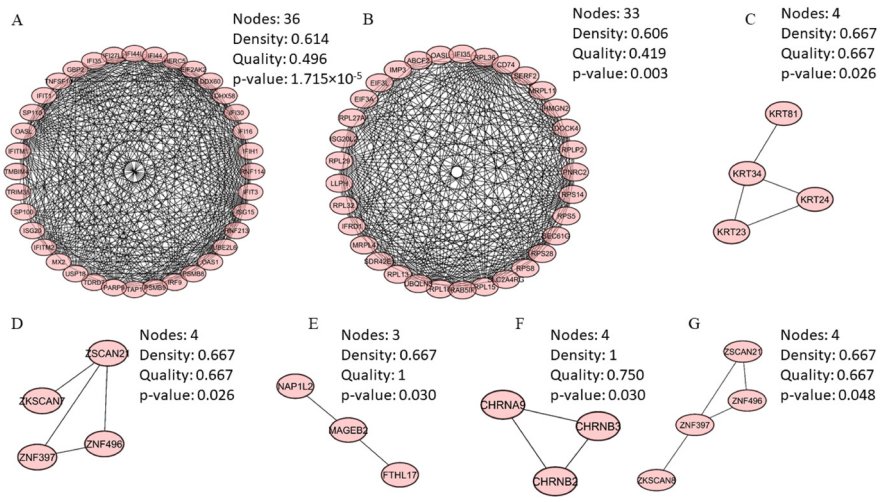


Figure 4. Detection of significant gene clusters in the PPI network using ClusterONE. For each cluster, the number of nodes, density, quality score, and statistical significance (p-value) are provided, indicating functional coherence and network modularity.

exploring potential therapeutic strategies through drug repurposing or targeted drug development (Table 2).

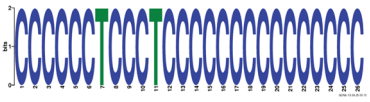
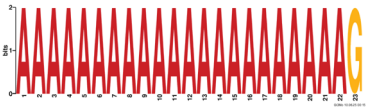
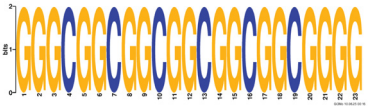
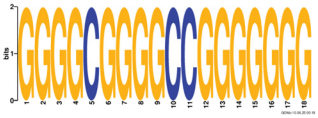
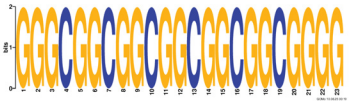
Promoter analysis of hub genes

Promoter motif analysis of the identified hub genes revealed several transcription factor binding sites and regulatory signatures that may be functionally relevant to the pathogenesis of SLE. As summarized in Table 3, GAPDH and PTEN promoters were enriched for motifs associated with transcription factor complexes and negative regulation of signal transduction. These findings suggest that both genes may exert regulatory effects not only through their canonical metabolic or tumor suppressor roles, but also by modulation of intracellular signaling cascades that are frequently dysregulated in autoimmune responses. Functional categories such as ATP binding, zinc ion binding, and protein dimerization further emphasize their involvement in transcriptional regulation and cellular metabolism. Interestingly, several ISGs (e.g., ISG15, IFI35, IFIT3 and IFITM2) demonstrated promoter motifs linked to transcription initiation from RNA polymerase II promoters and RNA metabolic processes, highlighting their role in amplifying interferon signatures, a well-established hallmark of SLE. The enrichment of motifs associated with immune stress responses and protein binding suggests that these ISGs may be tightly controlled at the transcriptional level to sustain chronic immune activation. Of note, ISG15 showed promoter enrichment in both transcription factor complex motifs and ATP binding categories, indicating its multifaceted regulation and potential role in cellular stress adaptation. Unexpectedly, genes such as IFIT3, IFITM2, and PTPRC exhibited promoter associations with noncanonical functional categories including olfactory receptor activity and sensory perception. While these motifs are classically linked to sensory pathways, emerging studies indicate that such transcriptional signatures can also reflect broader roles in G-protein–coupled receptor signaling and immune cell communication. In the context of SLE, these promoter features may represent cross-talk between immune regulation and nontraditional signaling pathways, further expanding the transcriptional landscape of disease. Collectively, the promoter motif analysis highlights the diverse and multi-layered regulation of hub

Table 2. Drug–target interaction analysis of identified hub genes in SLE

Drug	Drug group	Pharmacological action?	Target
4-(2-Aminoethyl)Benzenesulfonyl Fluoride	Experimental	Unknown	GAPDH
Adenosine-5-Diphosphoribose			
Artenimol	Approved, investigational		
Copper	Approved, investigational		
NADH	Approved, nutraceutical		
Omigapil	Investigational		
Thionicotinamide-Adenine-Dinucleotide	Experimental		
Xanthinol	Approved, withdrawn	Yes	
Phosphatidylethanolamine	Experimental	Unknown	PTEN

Table 3. Promoter motif analysis of hub genes with predicted transcription factor binding sites and associated functional categories

Motif	Logo	Length (bp)	Top 5 specific predictions
ENSG00000111640|GAPDH		26	CC transcription factor complex BP negative regulation of signal transduction BP lung development MF protein homodimerization activity MF protein heterodimerization activity
ENSG00000119917|IFIT3		23	MF olfactory receptor activity BP sensory perception of smell BP regulation of organ growth BP transcription initiation from RNA polymerase II promoter
ENSG00000171862|PTEN		23	CC transcription factor complex BP anterior/posterior pattern formation BP negative regulation of signal transduction MF ATP binding CC nucleolus
ENSG00000185201|IFITM2		12	MF olfactory receptor activity BP sensory perception of smell BP regulation of organ growth BP transcription initiation from RNA polymerase II promoter BP mRNA metabolic process
ENSG00000187608|ISG15		18	CC transcription factor complex BP anterior/posterior pattern formation BP negative regulation of signal transduction MF ATP binding CC nucleolus
ENSG00000262418|PTPRC		19	MF olfactory receptor activity BP sensory perception of smell BP G-protein coupled receptor protein signaling pathway BP defense response
ENSG00000284792|PTEN		23	CC transcription factor complex BP negative regulation of signal transduction MF ATP binding CC nucleolus MF zinc ion binding

BP:Biological process; CC: Cellular component; MF: Molecular function.

genes in SLE, reinforcing their contribution to aberrant immune signaling, stress response, and transcriptional reprogramming (Table 3).

Discussion

In this study, we conducted an integrative bioinformatics analysis to explore the molecular landscape of SLE using gene expression data derived from peripheral blood samples. Our approach combined differential expression analysis, functional enrichment, PPI network construction, hub gene identification, clustering of gene modules, and drug-target interaction prediction. The findings provide valuable insights into the complex immunopathology of SLE and highlight potential targets for therapeutic intervention.

The GO and Reactome pathway enrichment analyses revealed that the DEGs in SLE patients are predominantly involved in immune-related biological processes. Notably, pathways such as the innate immune system, interferon signaling, cytokine signaling, and immune system regulation were among the most enriched. This is consistent with previous studies that have established the central role of type I interferon responses and chronic immune activation in SLE pathogenesis. The upregulation of interferon-stimulated genes (ISGs) such as IFI35, IFIT3, and OAS1 within our dataset reinforces the concept of the "interferon signature" that characterizes many SLE patients and correlates with disease activity and severity (21-23).

The cellular component analysis showed that DEGs are primarily localized to intracellular organelles, cytoplasmic structures, and the endoplasmic reticulum, suggesting disturbances in protein processing, signaling cascades, and intracellular immune responses. Meanwhile, molecular function analysis indicated a dominance of protein binding activities, further supporting the hypothesis that dysregulated PPIs play a crucial role in the immunological aberrations observed in SLE.

The construction of a PPI network followed by topological analysis allowed for the identification of key hub genes-proteins with high centrality and potential regulatory influence within the network. Among these, GAPDH, PTEN, UBA52, and PTPRC emerged as prominent nodes. Interestingly, GAPDH, a classical glycolytic enzyme, is

increasingly recognized for its non-metabolic roles in inflammation, apoptosis, and nuclear signaling functions highly relevant to autoimmune pathophysiology. Elevated anti-GAPDH autoantibodies are found in SLE patients, correlating with increased disease activity scores (SLEDAI-2K), erythrocyte sedimentation rate, and serum IgG/IgM. The presence of these antibodies is related to a more active disease state and elevated inflammation markers in SLE patients, although anti-GAPDH autoantibodies were also associated with a decreased incidence of lupus nephritis (24,25). PTEN, a tumor suppressor and negative regulator of the PI3K-AKT pathway, also plays an immunomodulatory role and may influence T cell tolerance and survival, processes often dysregulated in SLE (26). ISG15, IFI35, OASL, IFIT3, MX2, IFITM2 are ISGs highly expressed in SLE. Their upregulation is associated with SLE disease activity, and they are considered potential biomarkers and therapeutic targets. ISG15 is connected to enhanced type I IFN response; IFIT3 and IFI35 are overexpressed and their levels decrease with improvement, while OASL and MX2 are also upregulated in SLE. These gene products are involved in heightened immune responses, a hallmark of lupus pathogenesis. ISG15 is an ubiquitin-like protein induced by type I IFNs and cellular stress. It exists both intracellularly and as a secreted extracellular protein. Intracellularly, ISG15 can conjugate to target proteins (ISGylation), affecting their stability, localization, or degradation. This regulates immune signaling and the cellular response to stress. Extracellular (secreted) ISG15 acts like a cytokine, promoting the production of IFN-γ by T cells and stimulating natural killer cell proliferation and cytotoxicity. Previous studies also found that, ISG15 modulates autophagy, mitochondrial function, and inflammatory responses. Autoimmune relevance; dysregulation and secretion of ISG15 are implicated in increased inflammation, and ISG15-positive plasma cells provide proinflammatory signals in human autoimmunity (27, 28). IFI35 is an interferon-inducible protein with dual roles. It negatively regulates the host antiviral IFN response, specifically by binding and inhibiting RIG-I (a pattern recognition receptor), leading to reduced IFN-β production. It can be released as a DAMP (damage-associated molecular pattern) promoting inflammatory responses. Moreover, IFI35 has been associated with promoting inflammation in chronic kidney disease and lupus nephritis by the activation of CD8 T cells and inflammatory signaling pathways (29,30). It influences immune evasion by affecting autophagy-lysosomal degradation of MHC-I, thereby potentially impairing antigen presentation and immune surveillance. In autoimmunity, OASL overexpression in CD4 T cells increases expression of CD40L and CD70 via enhanced DNA hydroxymethylation, promoting T-cell activation and aberrant immune responses, like in systemic sclerosis. Elevated OASL contributes to dysregulated T-cell activation and can serve as a biomarker or therapeutic target in autoimmune diseases (31). Furthermore, IFIT3 promote microglia polarization toward the M1 pro-inflammatory phenotype (linked to neuroinflammation and multiple sclerosis) and modulate the activity of immune checkpoints and contributing to immune infiltration in inflammatory conditions (32). In addition, MX2 is a dynamin-like GTPase induced by interferons, it participates in antiviral defense and immune modulation. MX2 is strongly associated with the activation of Toll-like receptor, NF-κB, and NOD-like receptor pathways. It increases neutrophil infiltration, high MX2 expression in SLE blood samples correlates with disease severity and neutrophil-mediated inflammation. Therefore, MX2 acts as a biomarker for disease activity (particularly in SLE), likely contributing to inflammation by promoting neutrophil recruitment and activation (33).

Using ClusterONE, we identified several statistically significant gene clusters, including densely connected modules enriched in ISGs, ribosomal proteins, keratin family members, zinc finger transcription factors, and neuronal receptor subunits. These modules likely represent coordinated transcriptional programs contributing to disease-specific immune responses, cell signaling, and tissue-specific manifestations (34,35). The identification of a keratin-related cluster, for instance, may reflect the involvement of cutaneous pathways in patients with skin-dominant lupus (36). Similarly, the zinc finger and acetylcholine receptor clusters suggest a broader network of immune regulation and neuroimmune interactions (37).

The drug-target interaction analysis provided translational value to our findings. Several compounds were identified as potential modulators of key hub proteins, most notably GAPDH. Drugs such as artenimol, omigapil, and xanthinol, although investigational or withdrawn in some contexts, could serve as a basis for repurposing strategies if their effects on immune regulation are further validated. Likewise, 4-(2-aminoethyl) benzenesulfonyl fluoride (AEBSF) is a serine protease inhibitor that impairs IL-12-induced activation of inflammatory mediators such as pSTAT4β, NFκB, which are involved in inflammation. As inflammation is a key component in SLE, AEBSF's anti-inflammatory properties may help reduce disease activity (38). Correspondingly, adenosine-5-diphosphoribose, which is involved in PARP signaling and DNA repair, has been linked to the regulation of cellular stress and apoptosis, processes frequently dysregulated in lupus pathogenesis (39). Artenimol (dihydroartemisinin derivative) also demonstrates immunomodulatory and anti-inflammatory properties, suggesting its potential utility in suppressing aberrant immune activation in lupus. Metabolic regulation represents another important target in SLE (40,41). Molecules such as NADH and thionicotinamide-adenine-dinucleotide are essential cofactors in mitochondrial redox reactions, and their modulation could counteract the mitochondrial dysfunction and oxidative stress commonly

reported in lupus patients (42,43). Copper, a trace element, is tightly linked to oxidative metabolism and immune function, and its balanced availability may support antioxidant defenses in SLE (44). Omigapil, an anti-apoptotic and neuroprotective agent, may help in reducing cell death associated with chronic inflammation in lupus. Phosphatidylethanolamine, a membrane phospholipid involved in autophagy and immune cell regulation, could influence both T-cell survival and inflammatory signaling (45). Taken together, these compounds, although not yet established as standard therapies, illustrate diverse molecular strategies, ranging from immune modulation and oxidative stress reduction to vascular protection and metabolic rebalancing, that could be relevant for improving outcomes in SLE.

Conclusion

In this study, we conducted an integrative transcriptomic and network-based analysis to uncover the molecular landscape of SLE. We identified 1,450 dysregulated genes, many of which were enriched in innate immune responses, interferon signaling, cytokine-mediated pathways, and signal transduction processes, reaffirming the central role of type I interferon signature in SLE pathogenesis. Network-based analysis highlighted several hub genes including GAPDH, PTEN, ISG15, IFI35, IFIT3, and MX2 as critical regulators connecting immune activation, metabolic control, and stress response. These hub genes are consistent with previously reported immunopathological features of SLE, but also reveal novel molecular connections that could serve as potential biomarkers. Furthermore, drug–target interaction analysis suggested that compounds such as artenimol, omigapil, NADH, 4-(2-aminoethyl) benzenesulfonyl fluoride, xanthinol, copper, and phosphatidylethanolamine may modulate these hub proteins and associated pathways. Although these findings are derived from in-silico predictions, they provide attractive hypotheses for drug repurposing strategies and therapeutic innovation. Particularly, GAPDH-targeting compounds such as artenimol and omigapil highlight novel opportunities to influence immune dysregulation and inflammation in SLE. Overall, our findings shed light on the complex immunopathology of SLE, introduce candidate biomarkers for disease activity, and suggest drug repurposing opportunities that warrant further exploration. Nevertheless, these results require rigorous validation in molecular (*in-vitro*) assays and animal (*in-vivo*) models to establish their translational potential and clinical relevance.

Limitations and future directions

While the present study provides meaningful insights into the molecular underpinnings of SLE, several limitations must be acknowledged. First, the analysis was conducted on a single microarray dataset with a relatively small sample size, which may limit the generalizability of the findings. Second, although our approach incorporated multiple bioinformatics tools and databases, all results remain computational and lack experimental validation. Furthermore, gene expression data alone cannot fully capture the post-transcriptional and post-translational regulatory mechanisms involved in SLE pathogenesis.

Future research should aim to validate the identified DEGs and hub genes using independent cohorts and complementary techniques such as qPCR, proteomics, or single-cell RNA sequencing. Functional studies, both in vitro and in vivo, are also necessary to confirm the biological relevance of the predicted gene modules and drug-target interactions. Integration with additional omics layers (e.g., epigenomics, metabolomics) and clinical data (e.g., disease activity scores, treatment response) could further refine the molecular stratification of SLE and enable the development of personalized therapeutic strategies.

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Authors' contribution

Conceptualization: Forouzan Amerizadeh.
Data curation: Arman Hosseini and Mozhdeh Ghamari.
Formal analysis: Forouzan Amerizadeh.
Funding acquisition: Forouzan Amerizadeh.
Investigation: Mozhdeh Ghamari, Arman Hosseini.
Methodology: Forouzan Amerizadeh.
Project administration: Mozhdeh Ghamari.
Resources: Forouzan Amerizadeh.
Software: Forouzan Amerizadeh.
Supervision: Mozhdeh Ghamari.
Validation: Mozhdeh Ghamari.
Visualization: Forouzan Amerizadeh.
Writing–original draft: Mozhdeh Ghamari, Arman Hosseini.
Writing–review & editing: Forouzan Amerizadeh.

Conflicts of interest

The authors declare that they have no competing interests.

Data availability statement

The data that support the conclusions of this study can be made available by the corresponding author upon a reasonable request.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki. The research was approved by the Ethics Committee of Mashhad University of Medical Sciences (Ethical code# IR.MUMS.IRH.REC.1403.224). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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