MALAYSIAN JOURNAL OF SCIENCE
MJS
ISSN 1394 - 3065

MAHSA International Medical Sciences and Technology Conference (Mi-Med) 2024

Special issue

Malaysian Journal of Science 44 (Special Issue 1): 47-54 (December 2025)

https://mjs.um.edu.my

Bioinformatics Analysis of Potential Biomarkers for Lupus Nephritis

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Abstract: Lupus Nephritis (LN) is a complication of Systemic Lupus Erythematosus affecting the kidney. The purpose of this study was to identify signalling pathways and hub genes involved in the pathogenesis of LN. Methods: The mRNA expression profiles of LN were obtained from the Gene Expression Omnibus database, and differentially expressed genes (DEGs) were identified using the online tool GEO2R. Enrichment analysis was conducted in DAVID. The Protein-Protein Interaction network of DEGs was constructed in STRING, and hub genes were identified with Cytoscape. The hub genes were validated using differentially expressed proteins (DEPs) from proteomics data to identify potential biomarkers for LN. Results: A total of 138 DEGs were identified, primarily associated with immune response, neutrophil chemotaxis, and antimicrobial humoral immunity. In KEGG analysis, the NOD-like receptor signalling pathway and the Cytokine-cytokine receptor interaction pathway were mainly involved. Nine hub genes of LN, including *Ifit1, Ifit3, Ifih1, Ifi44, Irf7, Irf9, Oasl1, Stat1*, and *Usp18* were identified. Conclusion: *Ifi44* and *Stat1* were expressed in both DEGs and DEPs. *Ifi44* and *Stat1* may be potential biomarkers and therapeutic targets for LN.

Keywords: Lupus Nephritis, bioinformatics, proteomics, biomarker.

1. Introduction

Lupus Nephritis (LN) is a complication of Systemic Lupus Erythematosus (SLE) associated with kidney damage. As the most common and serious complication of SLE, the pathological mechanism of kidney damage in LN remains complex (Lech & Anders, 2013; Nicolaou et al., 2020). Among patients with SLE, kidney disease-related mortality is significantly higher in patients with LN than in patients without nephritis (Parikh et al., 2020). Renal biopsy is the gold standard for diagnosing LN. The renal biopsy results can help assess renal pathology, disease activity, and prognosis (Giannico & Fogo, 2013; Saxena et al., 2011), but it is an invasive procedure that has the potential to cause harm (Mou et al., 2024). Therefore, exploring new biomarkers in the blood of LN patients is particularly important for diagnosing and treating LN.

In the past decade, multiple omics studies, such as genomics, transcriptomics, proteomics, and metabolomics, have examined the diagnosis, treatment, and prognostic analysis of kidney diseases (Zhou et al., 2023). Currently, integrating bioinformatics with renal and urinary proteomics studies has been developed as a method for diagnosing renal diseases (Paul et al., 2020). In a study of cross-species transcriptional networks of LN-prone mice and human LN, analysing this bidirectional information provides a new approach for diagnosing and treating LN (Berthier et al., 2012). Additionally, in an association study using single-cell RNA sequencing and proteomics, COL6A3 was identified as a biomarker and therapeutic target for diagnosing LN (Mou et al., 2024). Through multi-omics studies, the pathogenesis and progression of LN can be revealed from a novel perspective, aiding further exploration of new diagnostic and treatment strategies for LN.

In this study, differentially expressed genes (DEGs) from transcriptomics in mice with LN were validated using differentially expressed proteins (DEPs) from proteomics data to identify potential biomarkers for LN.

2. Materials and methods

2.1 Overview of Datasets Collection

The keywords Lupus Nephritis were searched in the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/); the datasets must have both LN and control groups. We obtained 4 LN gene expression profile datasets from the GEO database. GSE27045 was submitted by Bethunaickan et al. (2011), and GSE86423, GSE86424, and GSE86425 were submitted by Gardet et al. (2016). The gene expression profiles of renal macrophages in 6 pre-nephrotic control mice and seven nephritis NZB/W mice were obtained in GSE27045. GSE86423 included gene expression profiles of 3 control mice and 30 nephritis NZB X NZW F1 mice. GSE86424 included 40 control mice, 40 Pristane-induced nephritis SNF1 (SWR X NZB) mice, and 8 SNF1 (SWR X NZB F1) mice with spontaneous nephritis. GSE86425 included 51 control mice and 44 Pristane-induced nephritis SNF1 (SWR X NZB F1) mice.

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Received: May 11, 2025
Accepted: July 17, 2025
Published: December 12, 2025

DOI: https://doi.org/10.22452/mjs.vol44sp1.8
Malaysian Journal of Science 44 (Special Issue 1): 47-54 (December 2025)

The proteomic data were uploaded by Wen et al. (2024) on https://pubs.acs.org/doi/10.1021/acs.jproteome.3c00558. The raw data were stored in Proteomexchange (https://www.proteomexchange.org). The search number was PXD046815. This study included 40 female mice that were divided into four groups (n = 10): normal C57BL/6 control group; untreated MRL/lpr lupus; prednisone positive control MRL/lpr lupus and artesunate-treated MRL/lpr lupus groups.

2.2 Identification of common differentially expressed genes (CDEGs)

GEO2R is an online analysis program based on the R language in NCBI. We divided the samples into a control group and an LN group, and selected DEGs in each chip according to the default scheme of the platform. P value < 0.05 and |logFC|≥1 was set as the threshold for screening DEGs. The DEGs of 4 datasets were intersected by a Venn diagram to screen the CDEGs in the four datasets.

2.3 Enrichment analysis of CDEGs

Enrichment Analysis of CDEGs using the online tool DAVID (Huang et al., 2009) for Gene Ontology (The Gene Ontology Consortium et al., 2021) and the Kyoto Encyclopedia of Genes and Genomes pathway (Kanehisa et al., 2021), and the online tool bioinformatics (https://www.bioinformatics.com.cn) (Tang et al., 2023) was used for visualization of the results.

2.4 Construction of Protein-Protein Interaction (PPI) network and identification of hub genes

The CDEGs were imported into the online database String (https://string-db.org/) (Szklarczyk et al., 2021) to construct the PPI network and perform cluster analysis, and the visualization of the PPI network was created in Cytoscape (Version 3.10.2). The MCODE plugin of Cytoscape was used to identify the significant gene modules in CDEGs, and the cytoHubba plugin was used to identify the TOP10 genes (Betweenness) in CDEGs. The intersection of these two methods was considered as hub genes in LN.

2.5 Identification of differentially expressed proteins (DEPs)

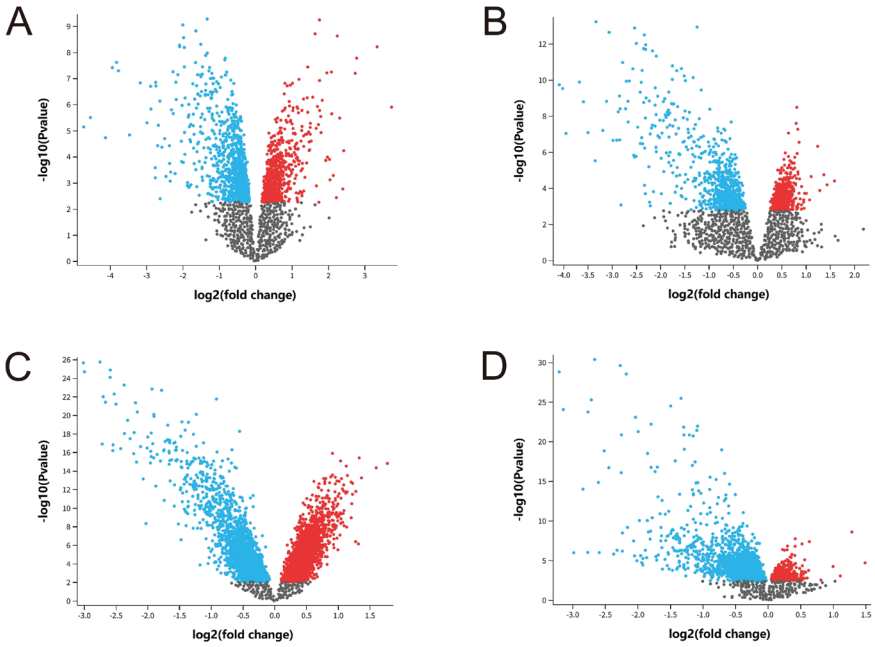

Figure 1. The volcano map of DEGs between LN and normal control of 4 datasets. (A) Volcano maps of GSE27045. (B) Volcano maps of GSE86423. (C) Volcano maps of GSE86424. (D) Volcano maps of GSE86425. Red dots represent up-regulated gene expression; blue dots represent down-regulated gene expression; black dots represent that these genes have no significant difference in LN. The horizontal axis indicates the fold change of gene expression in LN compared to normal control, and the vertical axis indicates the significance of the P. Value.

P <0.05 and | log2FoldChange |> 1 were set as thresholds for screening proteomic data results. DEPs were screened between the LN and the normal control.

2.6 Screening for potential biomarkers

The intersection of hub genes and DEPs was used to screen the potential biomarkers for LN.

2.7 Construction of mRNA-miRNA interaction

The hub genes were imported into the NetworkAnalyst (Zhou et al., 2019) database to predict the mRNA-miRNA interactions. The miRNAs interacting with the hub genes were identified.

DOI: https://doi.org/10.22452/mjs.vol44sp1.8
Malaysian Journal of Science 44 (Special Issue 1): 47-54 (December 2025)

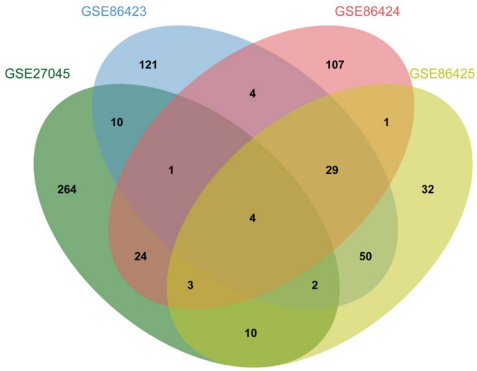

Figure 2. The Venn diagram of the CDEGs.

results showed that these CDEGs were primarily associated with immune response, neutrophil chemotaxis, and antimicrobial humoral immunity (Figure 3).

3.4 KEGG pathway enrichment analysis

The enrichment analysis of the KEGG pathway for CDEGs was performed, and 40 signaling pathways were obtained. These signal pathways were analyzed by KEGG secondary classification (Kanehisa et al., 2023). Five types of signaling pathways were obtained, including genetic information processing, environmental information processing, cellular processes, organic systems, and human diseases (Figure 4).

3.5 PPI network

The PPI network of the CDEGs was obtained by String, and the PPI network was used with Cytoscape plug-ins for visualization (Figure 5).

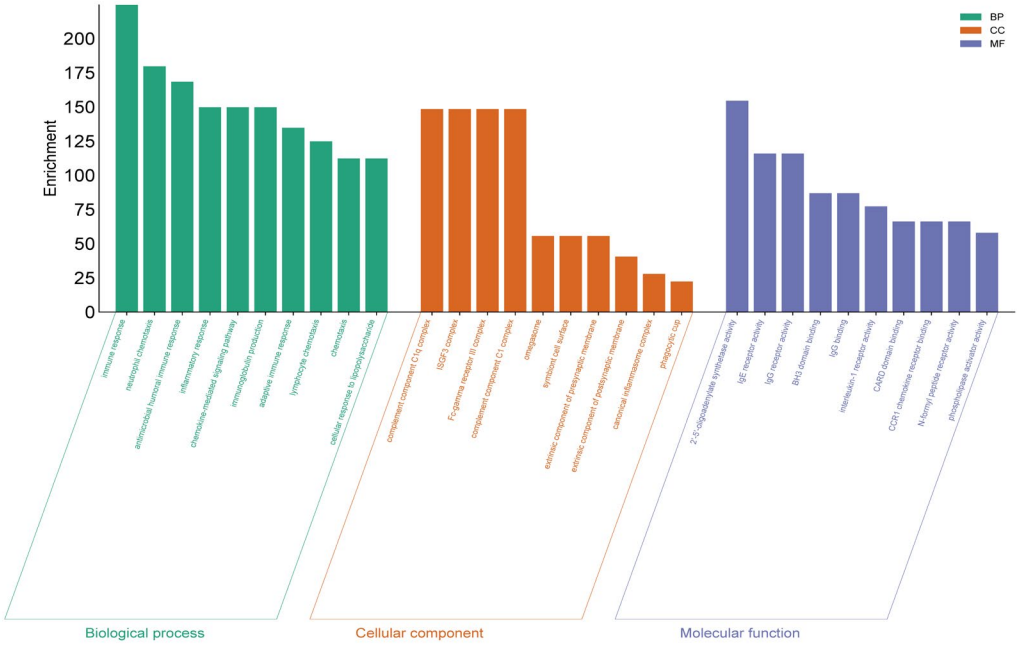

Figure 3. The GO enrichment analysis of CDEGs: The horizontal axis indicates the name of Biological Process, Cell Component and Molecular Function, and the vertical axis indicates the number of Biological Process, Cell Component and Molecular Function.

3. Results

3.1 The volcano map of DEGs

There are 318 differentially expressed genes (DEGs) in GSE27045, 221 DEGs in GSE86423, 173 DEGs in GSE86424, and 131 DEGs in GSE86425 (Figure 1).

3.2 Common differentially expressed genes (CDEGs)

The screening thresholds were set as $P < 0.05$ and $|\log FC| \geq 1$. The DEGs of the four datasets were intersected by a Venn diagram, and a total of 138 CDEGs were identified (Figure 2).

3.3 GO enrichment analysis

GO enrichment analysis includes biological processes, cell components, and molecular functions. The enrichment analysis

3.6 Hub gene of LN

The Cytoscape's MCODE plugin found three significant modules with 65 genes. Moreover, the cytoHubba plugin identified the TOP 10 genes. A Venn diagram was used to analyze the overlapping genes. Nine hub genes were identified, including *Ifit1, Ifit3, Ifih1, Ifi44, Irf7, Irf9, Oasl1, Stat1* and *Usp18* (Figure 6).

3.7 Potential biomarkers of LN

Through the analysis and selection by the setting thresholds, 211 DEPs were identified from the proteomic data. The nine hub genes and 211 DEPs were used in a Venn diagram to analyze the overlapping genes, and *Ifi44* and *Stat1* overlapped in both CDEGs and DEPs. *Ifi44* and *Stat1* were considered as the potential biomarkers of LN (Figure 7).

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Malaysian Journal of Science 44 (Special Issue 1): 47-54 (December 2025)

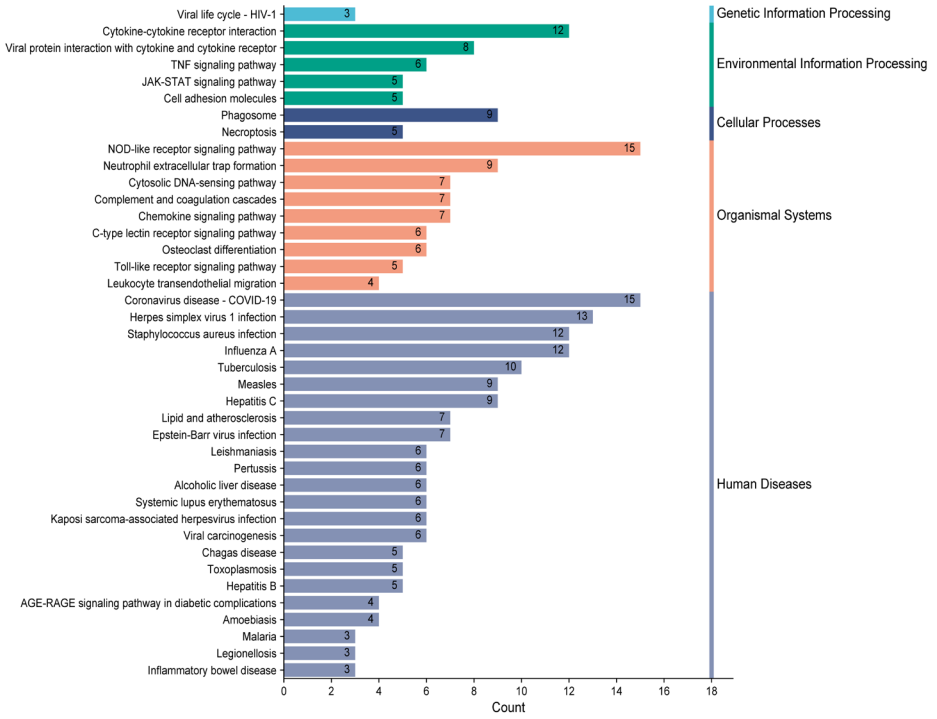

Figure 4. The secondary classification KEGG enrichment analysis of CDEGs. The horizontal axis indicates the count of signalling pathway, the left vertical axis indicates the name of signalling pathway, and the right vertical axis indicates the name of secondary classification.

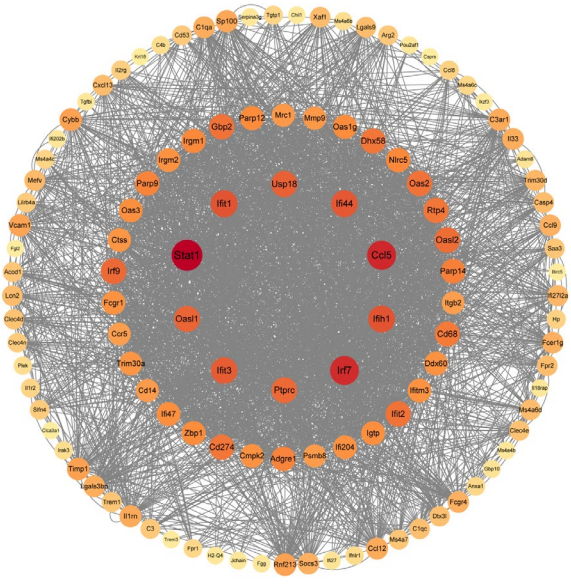

Figure 5. The PPI network of the CDEGs.

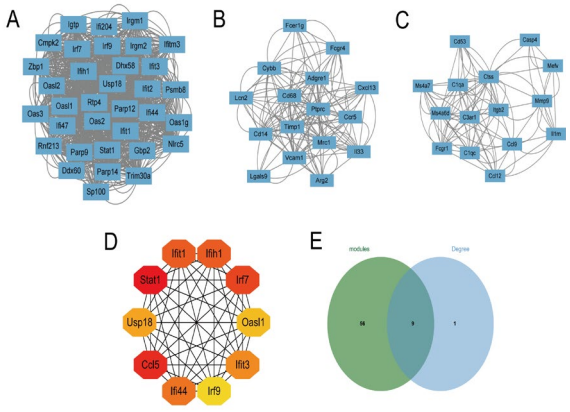

Figure 6. The CDEGs PPI network analysis. (A) Top 1 module identified by MCODE. (B) Top 2 module identified by MCODE. (C) Top 3 module identified by MCODE. (D) Top 10 genes identified by cytoHubba. (E) Hub genes identified by Venn diagram, the green circle represents the genes of MCODE three modules and the blue circle represents the cytoHubba Degree TOP10 genes.

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Malaysian Journal of Science 44 (Special Issue 1): 47-54 (December 2025)

3.8 Identification of mRNA-miRNA interaction

The mRNA-miRNA interactions were constructed by importing *Ifi44* and *Stat1* into the NetworkAnalyst database. The mRNA-miRNA network was developed, and *Ifi44* interacted with nine miRNAs, including mmu-miR-574-5p and mmu-miR-599, while *Stat1* interacted with 22 miRNAs, such as mmu-miR-3082-3p and mmu-miR-351-5p (Figure 8).

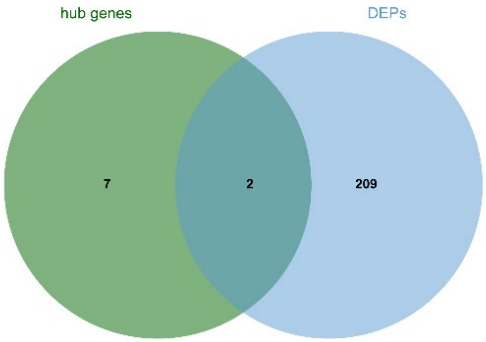

Figure 7. Venn analysis of hub genes and DEPs. The green circle represents the hub genes and the blue circle represents DEPs. The intersection of these two circles represents the potential biomarkers.

4. Discussion

LN is the most common and serious complication of SLE, and the incidence of LN is closely associated with increased mortality in SLE patients (Davidson et al., 2015; Lin et al., 2023). At present, single-omics studies have been widely employed in the study of LN, but they remain insufficient to reveal the complex mechanisms of LN fully. Therefore, integrating multi-omics techniques to investigate the pathophysiological mechanism of LN will contribute to a more comprehensive and deeper understanding of LN.

In this study, we identified 138 CDEGs associated with LN. These CDEGs mainly involve biological processes such as immune response, neutrophil chemotaxis, and antimicrobial humoral immune response. LN is characterized by autoimmune response and inflammation of the kidney, and its onset is closely related to the abnormal activation of the immune system (Tang et al., 2023; Arazi et al., 2019). Neutrophil dysregulation is involved in the immune disturbance and vascular injury in SLE; the immune complex can induce neutrophil activation, which leads to the aggravation of inflammation and renal tissue injury (Mistry et al., 2019; Yu et al., 2022). Humoral immunity mediates the initiation and expansion of inflammatory response through autoantibodies, and the activated immune response and inflammation play an important role in the development of LN (Arora et al., 2017; Conti et al., 2011).

In the secondary classification results of the KEGG pathway, we found two key signalling pathways after excluding human diseases: the NOD-like receptor signalling pathway and Cytokine-cytokine receptor interaction. Studies have shown that the NOD-like receptor signalling pathway is related to the production of inflammatory factors; the inhibition of the NLRP3 signalling pathway can reduce the expression of inflammatory factors, thereby alleviating kidney injury (Zhang et al., 2018; Zhao et al., 2013). Cytokine-cytokine receptor interaction regulates the immune response, inflammation, and intercellular communication through the binding of cytokines and their receptors. Interleukin (IL) and tumour necrosis factor (TNF) are common cytokines; previous reports have shown that IL-35 affects the JAK-STAT signalling pathway, involved in the regulatory process of LN development (Cai et al., 2021). The activation of the TNF signalling pathway triggers the production of inflammatory cytokines, increasing kidney injury in LN (Qing et al., 2018).

Through the PPI network of CDEGs, we identified nine hub genes associated with LN, including *Ifit1, Ifit3, Ifih1, Ifi44, Irf7, Irf9, Oasl1, Stat1*, and *Usp18*. Studies have shown that the genes *Ifit1*, *Ifit3, Ifih1, Irf7,* and *Irf9* in lupus mice can induce the production and response of interferon, participating in the development of LN (Funabiki et al., 2014; Hu et al., 2016; Ikeda et al., 2017; Miyagawa et al., 2016; Thibault et al., 2008). The imbalance of macrophages is involved in the pathogenesis of SLE; researchers found that the expression of USP18 in monocytes of SLE patients was higher than that of normal controls. Further research found that *Usp18* can mediate cell polarization through M1 signalling (Lai et al., 2024). Another study showed that in the peripheral blood mononuclear cells of LN, the expression of USP18 is associated with disease activity (Shen et al., 2022). *Oasl1* is a member of the OAS gene family, participating in the immune response through interferon (Elkhateeb et al., 2016). In a chronic viral infection mouse model, the IFN-I negative regulator Oasl1 can inhibit T cell function and plays an important role in virus clearance (Lee et al., 2013). However, there are no reports of Oasl1 in LN.

In addition, *Ifi44* and *Stat1* were differentially expressed in DEPs and DEGs. IFI44 is a type I interferon (IFN)-inducible gene implicated in the pathogenesis of autoimmune diseases. In a TLR3-deficient mouse model infected with Friend retrovirus, the expression of the IFN-stimulating gene *Ifi44* was significantly decreased, suggesting that *Ifi44* is involved in the immune response to retrovirus infection by mediating the IFN pathway (Gibbert et al., 2014). The expression of IFI44 shows significant specificity in LN patients; studies have shown that IFI44 can be used as a candidate biomarker for the diagnosis of LN (Shen et al., 2021). Additionally, it has been reported that in naive CD4+T LN patients, they have higher expression of IFI44 due to DNA demethylation (Coit et al., 2015), and Mok et al. (2016) reported similar results, showing that methylation of IFI44 in CD4+T cells is significantly associated with LN development.

Stat1 is an important transcription factor involved in the interferon signalling pathway. In LN mice, knocking down Stat1 can inhibit the NLRP3 inflammasome and reduce inflammatory markers such as IL-1β and IL-18, thereby alleviating kidney injury

DOI: https://doi.org/10.22452/mjs.vol44sp1.8
Malaysian Journal of Science 44 (Special Issue 1): 47-54 (December 2025)

in LN mice (Zheng et al., 2024). Additionally, it has been reported that Stat1 is highly expressed in the kidneys of LN mice (Deng et al., 2021), while inhibiting Stat1 expression can alleviate glomerular proteinuria (Yiu et al., 2016). Studies have confirmed that STAT1 is significantly correlated with LN; the overexpression of miR-145 can inhibit STAT1 expression and participate in interferon-mediated signalling pathways (Lu et al., 2012). In another study, lncRNA RP11-2B6.2 participates in the pathogenesis of LN by mediating the IFN-I signalling pathway through the SOCS1 gene. Knocking down lncRNA RP11-2B6.2 promotes SOCS1 expression and inhibits STAT1 phosphorylation in the IFN-I pathway (Liao et al., 2019).

We constructed mRNA-miRNA networks to further explore the diagnostic value of Ifi44 and Stat1. MiRNAs mainly regulate gene expression at the post-transcriptional level. Previous studies have demonstrated that the LncRNA XIST/miR-381-3p/STAT1 axis may serve as a potential biomarker for LN (Chen et al., 2024). In another study, miRNA-155 promotes podocyte apoptosis by activating the JAK1-STAT1 signalling pathway (Pang et al., 2025). To our knowledge, there have been no reports on Ifi44 and miRNA in LN. Therefore, the mRNA-miRNA network constructed in this study enhances the understanding of Ifi44 and Stat1 in LN. On one hand, the expression of Ifi44, Stat1, and miRNAs such as mmu-miR-574-5p, mmu-miR-599, mmu-miR-3082-3p, and mmu-miR-351-5p can be used as biomarkers for diagnosing LN. On the other hand, by regulating the activity of miRNAs, new therapeutic methods can be developed, such as modulating Ifi44 and Stat1 expression by interfering with miRNA expression.

5. Conclusion

This study used bioinformatics combined with proteomics to identify key signalling pathways and hub genes involved in LN. The results show that Ifi44 and Stat1 may be potential biomarkers and therapeutic targets for LN. However, the findings of this study require confirmation through experimental verification.

5.1 Data availability statement

The Lupus Nephritis datasets GSE27045, GSE86423, GSE86424 and GSE86425 were downloaded from the Gene Expression Omnibus (GEO) database. Proteomics data is available on the website https://pubs.acs.org/doi/10.1021/acs.jproteome.3c00558. The raw data was stored in proteomexchange (https://www.proteomexchange.org), serial number is PXD046815.

6. Author contributions

This work was conceived by Zhao Liang and Zhiming Tang. Zhao Liang performed the experiments with the help from Suresh V Chinni and conducted the data analysis. Zhao Liang wrote the manuscript and Suresh V Chinni edited and revised the manuscript. All authors contributed to the article and approved the submitted version.

7. Declaration of competing interest

The authors have no conflicts of interest to disclose.

8. Acknowledgements

This work was supported by Research Foundation Ability Enhancement Project for Young and Middle aged Teachers in Guangxi Universities 2024KY0552. We thank Figdraw (www.figdraw.com) for generating the graphical abstract for this study.

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