ZBP1 is a significant pyroptosis regulator for systemic lupus erythematosus

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Background: Systemic lupus erythematosus (SLE) is a common autoimmune disease that affects all organs. Recently, several studies have shown that pyroptosis playsa significant process in the occurrence and progression of SLE. However, no study has investigated the association between pyroptosis genes and SLE. We conducted this study to examine this association.

Methods: The GSE11090, GSE20864, and GSE112087 gene microarrays of normal and SLE patient samples were downloaded from the Gene Expression Omnibus database. A differentially expressed gene (DEG) analysis was performed using the LIMMA package in R software. Log_2 fold change $|\log_{FC}| > 0.5$ and a false discovery rate (FDR) <0.05 setting for DEGs' screening value. We also performed an enrichment function analysis of the DEGs. To explore the role of pyroptosis genes in SLE, we selected pyroptosis genes that intersected with the DEGs for further analysis, we also examined the expression levels of the selected genes, their association with immune cell infiltration, and conducted western blotting and polymerase chain reaction analyses to confirm the selected genes expression levels in the SLE and normal samples.

Results: A total of 3,398 identical genes were obtained from 3 datasets for the differential analysis. 84 upregulated genes and 52 downregulated genes were identified in SLE. The enrichment function analysis revealed that DEGs act as key regulators of nicotinamide adenine dinucleotide (NADH) dehydrogenase activity, phospholipid scramblase activity, double-stranded ribonucleic acid (RNA) binding, and the interferon signaling pathway. We identified the SLE-related pyroptosis gene, Z-DNA binding protein 1 (*ZBP1*), by intersecting the DEGs of SLE and 40 pyroptosis genes. The differential analysis indicated that *ZBP1* was more highly expressed in SLE patients compared to normal samples (P<0.001). Additionally, the expression of *ZBP1* was higher in females than males (P=0.008). The SLE samples had different immune cell infiltration than the normal samples, and *ZBP1* was significantly correlated with immune cell infiltration in the SLE samples. Finally, the validation experiments results showed that *ZBP1* expression levels were significantly more highly expressed in female and SLE patients, than male and normal patients.

Conclusions: *ZBP1* may indicate that females have a high incidence rate of SLE, and it plays a significant role in the occurrence and progression of SLE.

Keywords: Pyroptosis; *ZBP1*; systemic lupus erythematosus (SLE)

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Introduction

Systemic lupus erythematosus (SLE) is characterized by the loss of autoantibodies, massive immune complex deposition, the activation of inflammation, and immunity, which results in different degrees of damage in different organs (1). The main hallmarks of SLE are losing control of immune tolerance and the sustained production of autoantibodies against nuclear autoantigens (2). Research on the pathogenesis of SLE has shown that several types of programmed cell death play significant roles in the process of SLE (3). In 1972, Kerr *et al.* first defined programmed cell death apoptosis (4). Subsequently, several types of programmed cell death, such as autophagy, NETosis, necroptosis, and pyroptosis, have been defined and widely investigated in different diseases.

The dysregulation of cell death and a decrease in the ability to clear death cells lead to damage-associated molecular patterns, and enhance inflammation, immunity activation and the generation of autoantigens, resulting in tissue and organ damage in SLE patients (5). As programmed cell death plays a critical role in SLE, we focused on the role of pyroptosis-related genes in SLE. Pyroptosis is a type of programmed cell death that is characterized by cell lysis and inflammation induced by various damage signals (6). Its main features are gasdermin family-mediated cell deformation and eventual lysis, which results in the release of cell contents, including interleukin (IL-)1β and IL-18 (3). Pyroptosis was first observed in Shigella flexneri-infected macrophages (7). The activation of pyroptosis triggers the assembly of the inflammasome sensor, which leads to inflammation (8). Pyroptosis plays a key role in various diseases (9-12). In relation to SLE, research has shown that abnormal cell death and the dysregulation of dead cell clearance induces the production of antinuclear antibodies and other aberrant immune responses (13).

Pyroptosis is a type of cell death, and the dysregulation of pyroptosis has been implicated in the pathogenesis of lupus nephritis (LN) (3,13). Research has confirmed that pyroptosis also significantly affects the progression of SLE, Faliti *et al.* found that restoring P2X7 activity in SLE patients could selectively limit the progressive amplification of pathogenic autoantibodies, which deteriorate patients' conditions (14,15). NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome, an inflammasome sensor that mediates pyroptosis, was found to be hyperactivated in patients with SLE and LN (16). In the presence of anti-double-stranded DNA (dsDNA) antibodies, dsDNA can induce the activation of the NLRP3 inflammasome (17). Similarly, NLRP3 inflammasome activation can also be triggered by the interaction of U1-small nuclear ribonucleoprotein (U1-snRNP) and anti- U1-snRNP antibodies (18,19). However, these studies only investigated the role of pyroptosis in SLE, and the process of pyroptosis is affected by many factors, such as pyroptosis-related genes. In this study, we examined pyroptosis-regulated genes to investigate the correlation between genes and SLE.

We present the following article in accordance with the STREGA reporting checklist (available at https://dx.doi.org/10.21037/atm-21-6193).

Methods

Original data

We downloaded three sets of gene microarrays (GSE11090, GSE20864, and GSE112087) from the Gene Expression Omnibus (GEO) database, including SLE and normal samples. After normalization and combination, a gene expression matrix of 122 normal samples and 239 SLE samples was obtained for further analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

The acquisition of DEGs

An analysis of gene differences between the SLE and normal samples was performed using the LIMMA package in R software. A $\log_2$ fold change $|\log_{FC}| > 0.5$ and a false discovery rate (FDR) <0.05 indicated that the genes were differentially expressed.

Enrichment analysis of DEGs

A gene set variation analysis (GSVA package) was conducted to analyse and identify significantly different Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways that were activated or inhibited in the SLE sample. The gene oncology (GO) enrichment analysis of the DEGs was conducted using the ClusterProfiler package.

Identifying the SLE-related pyroptosis gene

Forty pyroptosis-related genes in the pyroptosis signaling pathway from the gene set enrichment analysis (GSEA, https://www.gsea-msigdb.org/) were extracted and intersected with the SLE DEGs. We also analyzed the

expression of SLE-related pyroptosis genes in SLE and normal tissues, and their correlation with clinical traits.

Immunological infiltration analysis

We calculated the relative abundance of 22 immunocytes in the samples with the CIBERSORT algorithm, and analyzed the relationship between the immunocytes and SLE-related pyroptosis gene.

Validation experiments

Finally, we performed several validation experiments to confirm the finally selected gene expression levels between female and male SLE patients and normal patients.

Statistical analysis

All the statistical analyses were conducted using R software (version 4.0.3). The difference gene analysis used the LIMMA package. The following threshold was set: $|\log_{FC}|$ >0.5 and FDR <0.05. The Wilcoxon non-parameter test was used to compare two groups. The Spearman method was used for the correlation analysis A P value <0.05 indicated a statistically significant difference.

Results

DEGs and differential signaling pathways in SLE

A total of 3,398 identical genes were obtained from the three data sets for the differential analysis. *Figure 1A* shows a heatmap of the top 20 up/downregulated genes in SLE. Eighty-four upregulated genes and 52 downregulated genes were identified in SLE (see *Figure 1B*).

The enrichment analysis of the 136 DEGs revealed 10 significantly altered pathways, 6 of which were activated and 4 of which were inhibited in SLE (see *Figure 1C*).

GO enrichment analysis of DEGs in SLE

The biological process (BP) of the DEGs in SLE was mainly enriched in the defense response to the virus, the interferon-gamma–mediated signaling pathway, the type I interferon signaling pathway, the cellular response to type I interferon, and the response to type I interferon. The circle diagram shows the genes contained in the 5 BPs (see *Figure 2A*). The cell components were mainly enriched in the cell-substrate junction, focal adhesion, oxidoreductase complex, fibrillar center, and npBAF complex. The molecular function was mainly enriched in pattern recognition receptor activity, 4 iron, 4 sulfur cluster binding, NADH dehydrogenase activity, and phospholipid scramblase activity (see *Figure 2B*).

Acquisition of the SLE-related pyroptosis gene

We identified the SLE-related pyroptosis gene, *ZBP1*, by intersecting the DEGs of SLE with the 40 pyroptosis genes (see *Figure 3A*). The differential analysis indicated that *ZBP1* was more highly expressed in SLE patients compared to normal samples (P<0.001; see *Figure 3B*). Additionally, the expression of *ZBP1* was higher in females than males (P=0.008; see *Figure 3C*).

Analysis of immune infiltration in SLE and normal samples

The CIBERSORT algorithm was used to calculate 22 immunocells in 361 samples. *Figure 4A* shows the immune cell abundance of all the samples. *Figure 4B* shows the correlation between the 22 immunocell in the SLE patients, among them, resting dendritic cells and M2 macrophages had the highest negative correlations, and B memory cells and plasma were the most relevant (see *Figure 4B*). T cells CD8, monocytes, M1 macrophages, dendritic cells, eosinophils and neutrophils were more highly infiltrated in patients with SLE. While resting memory CD4 T cells, activated memory CD4 T cells, gamma delta T cells, and resting natural killer (NK) cells were lowly infiltrated in patients with SLE (see *Figure 4C*).

The relationship between gender and immunocell abundance in SLE patients

The immunocell abundance and gender difference analyses demonstrated that activated dendritic cells (P=0.039, *Figure 5A*), M1 macrophages (P=0.019, *Figure 5B*), and neutrophils (P=0.0032, *Figure 5C*) were more highly infiltrated in female patients than male patients.

The relationship between ZBP1 expression and immunocells

The results indicated that activated immunocell dendritic cells and M2 macrophages were positively correlated

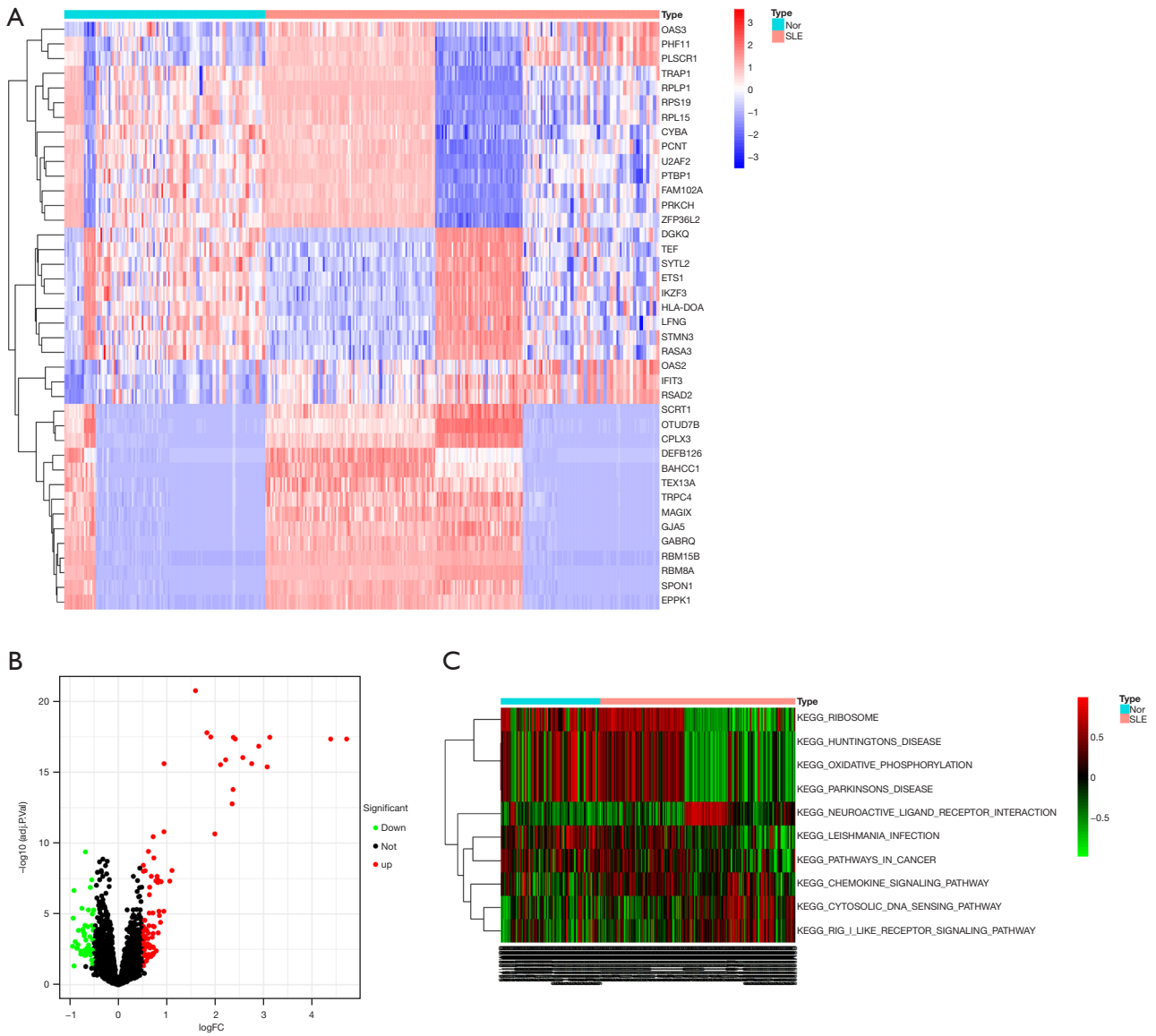

Figure 1 DEGs and differential signaling pathways in SLE. (A) Heatmap of the top 20 up/downregulated genes in SLE; (B) volcanic plot of DEGs in SLE; (C) heatmap of the dysregulated KEGG signaling pathways in SLE. DEGs, differentially expressed genes; KEGG, Kyoto encyclopedia of genes and genomes; SLE, systemic lupus erythematosus.

with the expression levels of *ZBP1*, but resting dendritic cells and monocytes were negatively correlated with the expression levels of *ZBP1* in SLE patients (see *Figure 6A-6D*). Additionally, activated immunocell plasma cells, CD4 memory T cells, resting CD4 memory T cells, and naive CD4 T cells were positively correlated with *ZBP1* expression (see *Figure 6E-6H*); however, CD8 T cells, follicular helper T cells, gamma delta T cells, and regulatory T cells were positively correlated with *ZBP1* expression (see *Figure 6I-6L*).

Validation experiments

To investigate the *ZBP1* expression levels in SLE and normal samples, we performed western blotting and polymerase chain reaction analyses to validate the expression of *ZBP1*, and the results showed that *ZBP1* was significantly more highly expressed in female and SLE patients than male and normal patients, respectively (see *Figure 7A-7C*).

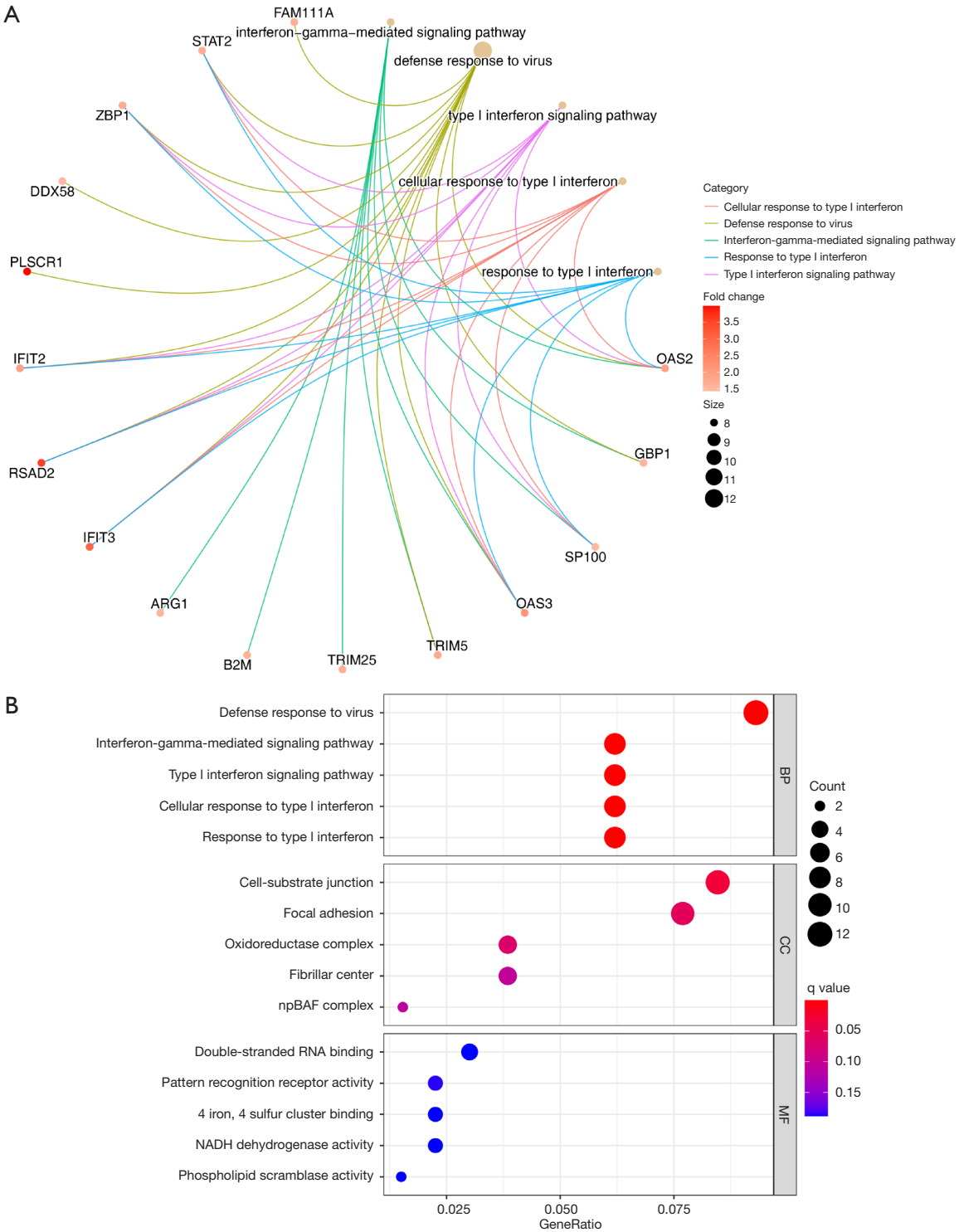

Figure 2 GO enrichment analysis of DEGs in SLE. (A) Circle diagram of the genes contained in the 5 BPs; (B) bubble diagram of the biological processes, cell components, and molecular functions of GO enrichment functions. BPs, biological processes, DEGs, differentially expressed genes; GO, gene oncology; SLE, systemic lupus erythematosus; BP, biological process; CC, cell components; MF, molecular function.

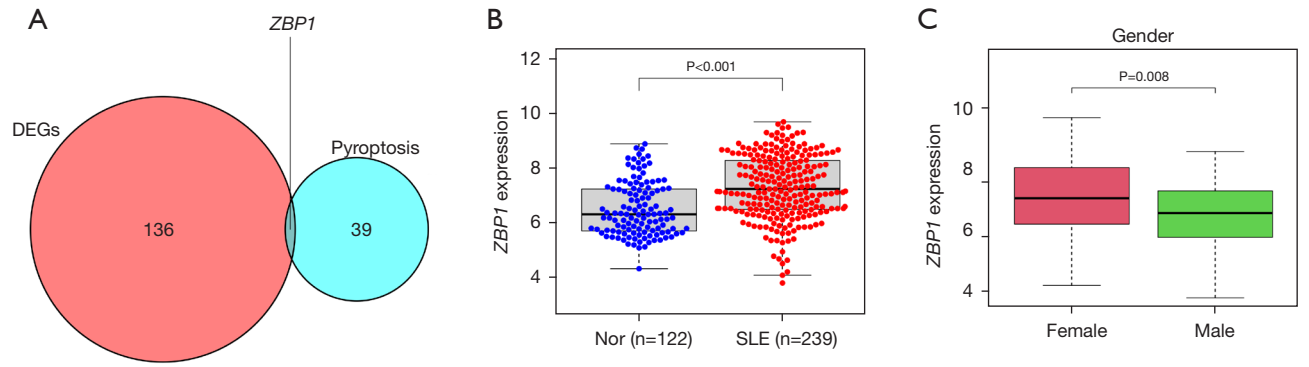

Figure 3 The expression and gender difference of the pyroptosis gene *ZBP1* in SLE. (A) Venn diagram of DEGs of SLE and pyroptosis genes; (B) expression levels of *ZBP1* in SLE blood samples and normal blood samples; (C) expression levels of *ZBP1* in male and female SLE samples. DEGs, differential expressed genes; SLE, systemic lupus erythematosus; *ZBP1*, Z-DNA Binding Protein 1.

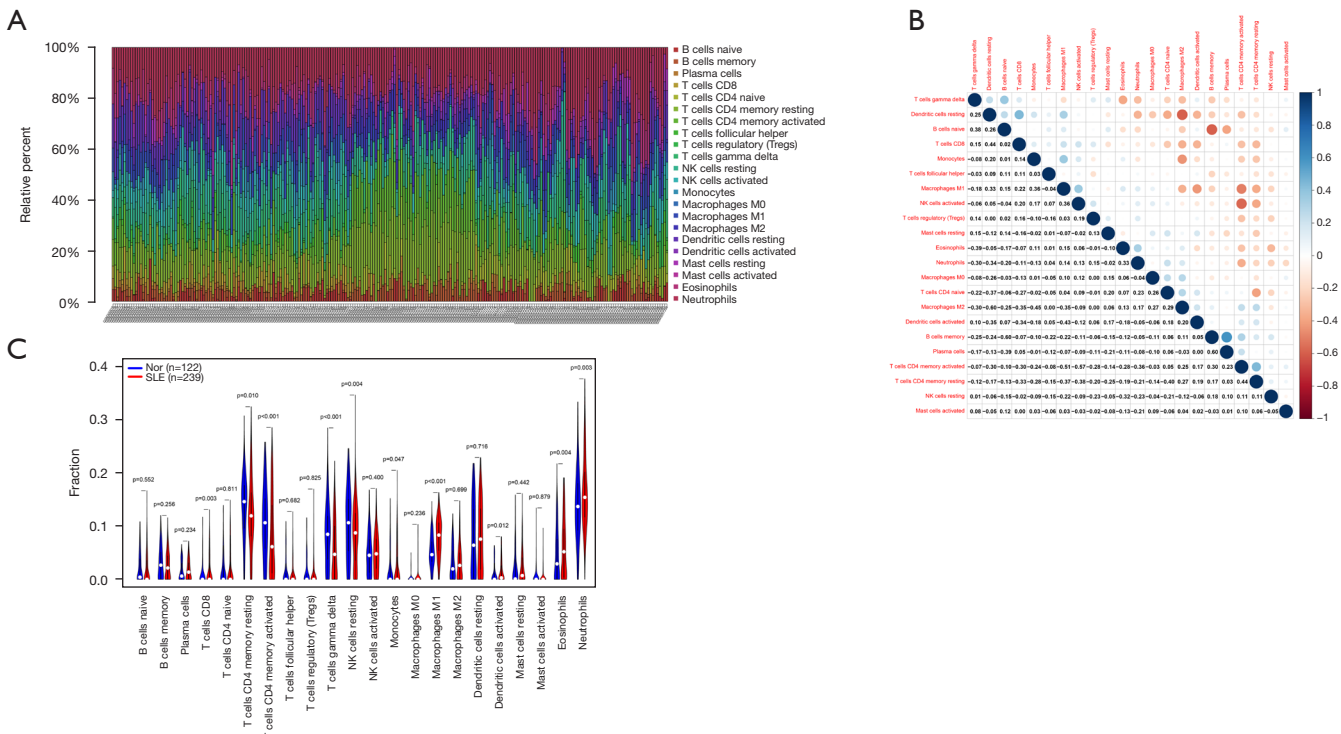

Figure 4 Analysis of immune infiltration in SLE and normal samples. (A) Histogram of the relative abundance of 22 immunocells in SLE and normal samples; (B) correlation heatmap between 22 immunocells; (C) Violin diagram of the differential expression of 22 immunocells between SLE and normal samples. SLE, systemic lupus erythematosus.

Discussion

SLE is an autoimmune disease, and it can damage several important organs, such as the brain, heart, kidneys, and lungs, and SLE patients suffer more during in these target organ complications. The epidemiology of SLE proves that it has a significant relationship with gender, and young women are at a higher risk than young men in terms of morbidity. Besides, the multiple underlying mechanisms of SLE have been classified. Among the various mechanisms, cell death plays a key role in SLE progression. The cell-

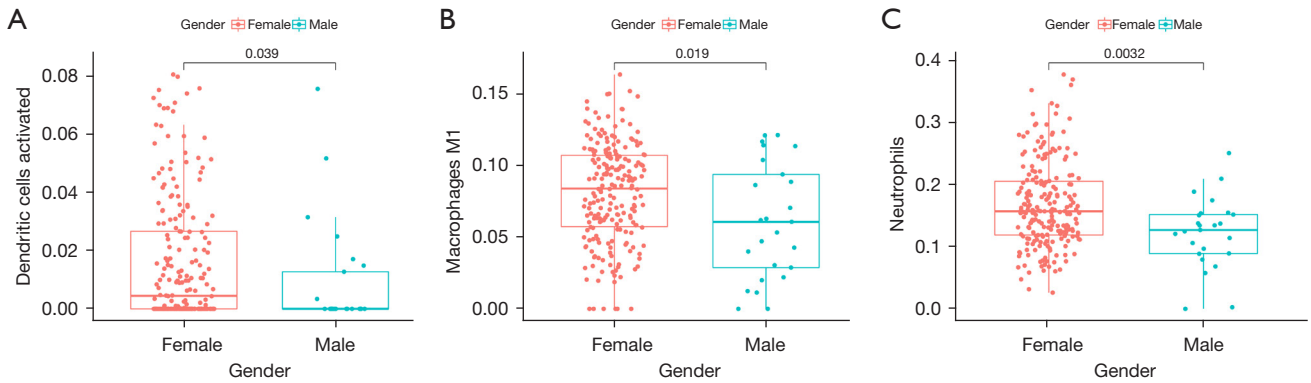

Figure 5 The relationship between gender and immunocell abundance in SLE patients. (A) Activated dendritic cells; (B) M1 macrophages; (C) neutrophils. SLE, systemic lupus erythematosus.

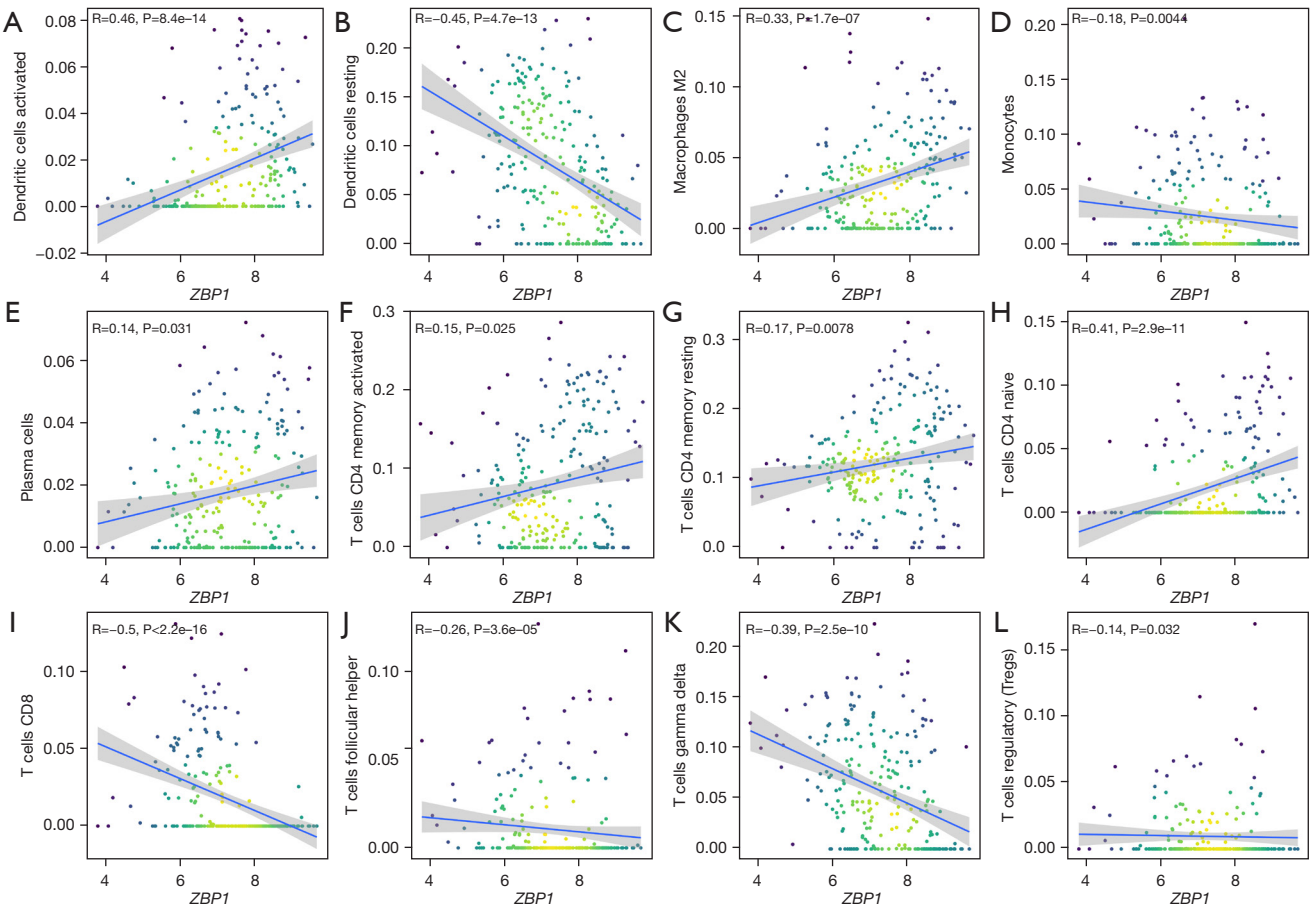

Figure 6 The relationship between *ZBP1* expression and immunocells. (A) Activated dendritic cells; (B) resting dendritic cells; (C) M2 macrophages; (D) monocytes; (E) plasma cells; (F) activated CD4 memory T cells; (G) resting CD4 memory T cells; (H) CD4 naïve T cells; (I) CD8 T cells; (J) Follicular helper T cells; (K) Gamma delta T cells; (L) regulatory T cells. *ZBP1*, Z-DNA Binding Protein 1.

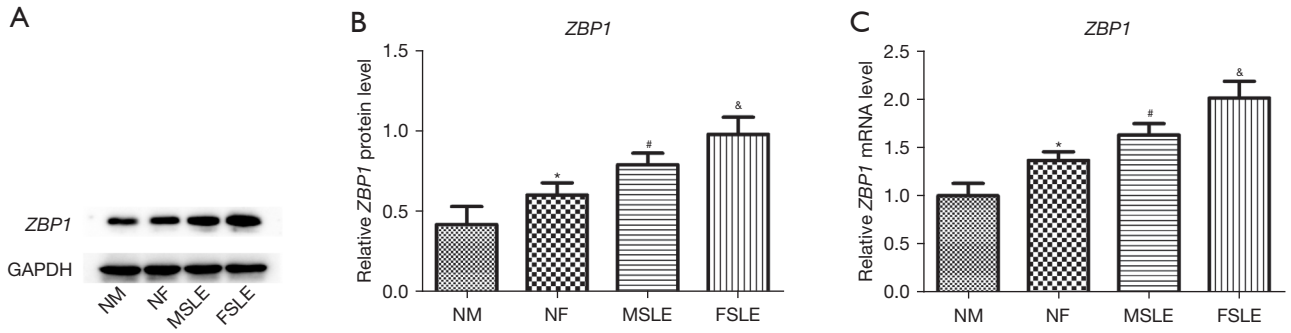

Figure 7 The validation experiments of *ZBP1*. (A,B) The western blot of *ZBP1*; (C) the quantitative real-time PCR of *ZBP1*. * represent no-SLE female samples; # represent male SLE patients samples, and & represent female SLE samples, respectively. *ZBP1*, Z-DNA Binding Protein 1; PCR, polymerase chain reaction.

type process induces inflammation, releases auto antigens, and leads to some diseases. Research of the pyroptosis process revealed that it is involved in multiple diseases, including SLE (20-22). This study explored pyroptosis gene expression levels in different samples, the fundamental biological functions of pyroptosis' DEGs, and pyroptosis gene' role in SLE.

In present study, the results showed that 136 DEGs were differentially expressed between the SLE and normal samples. The top DEGs included *OAS3*, *PHF11*, *PLSCR1*, *TRAP1*, *RPLP1*, *RPS19*, *RPL15*, *CYBA*, *PCNT*, *U2AF2*, *PTBP1*. Gao *et al.* revealed MALAT1 affects SLE by regulating the expression of OAS3 (23). Yamada *et al.* found that PHF11 is a regulator of inflammation (24). PPLSCR1 was observed to be overexpressed in monocytes in SLE samples (25). TRAP1 and RPLP1 play key roles in SLE progression (26,27). Regrettably, several genes have not been found to have an association with SLE, including *OAS3*, *PHF11*, *PPLSCR1*, *TRAP1*, and *RPLP1*. In the present study, we examined the enrichment functions of these DEGs, and found that NADH dehydrogenase activity, phospholipid scramblase activity, double-stranded RNA binding, and the interferon signaling pathway may be the most important biological functions. Suzuki *et al.* found that phospholipid scramblase (phospholipid scramblase 1) induces fibrin turnover and increases cell-surface phosphatidylserine exposure, promoting the risk of thrombus (25). Double-stranded RNA antibodies have also been investigated in SLE, and RNA antibody levels have been found to be associated with disease activity (28). Interferon has been shown to act as an important regulator of SLE, and interferon lambda affects the immune system and inflammation dysregulation (29).

Thus, DEGs play a key role in SLE. We selected pyroptosis genes for further analysis and examined the intersection between the pyroptosis genes and DEGs in the SLE samples. *ZBP1* was selected and we investigated its role in SLE. The results showed that *ZBP1* was significantly more highly expressed in SLE patients than normal patients, and the subgroup analysis revealed that females have higher *ZBP1* expression levels than males. *ZBP1* is a Z-DNA-binding protein type that can be induced via interferons (30). *ZBP1* can act as a regulator of interferon-induced necroptosis (31). Further, *ZBP1* is also an innate sensor for inflammation, and is a significant regulator of multiple disease processes, such as influenza virus infection, NLRP3 inflammasome, and proinflammatory responses (32,33). Takaoka *et al.* revealed that *ZBP1* is the ligand of double-strain DNA, and may have an association with autoimmune disease (34). However, the role of *ZBP1* in SLE is still unclear.

As autoimmune disease and *ZBP1* have a significant relationship with inflammation and necroptosis, and immune cells act as important factors in these processes, we investigated the relationship between *ZBP1* and immune cell infiltration. The analysis results showed that *ZBP1* is significantly associated with several types of immune cell infiltration, including dendritic cell, monocyte, macrophage, CD4 T cell, and CD8 T cell infiltration. *ZBP1* is negatively correlated with regulatory T cells, and many studies have shown regulatory T cells play a key role in SLE progression (35-37). Several studies have revealed that SLE patients have increased CD8 T cell levels, which induce autoantibody production, resulting in organ damage (38,39). However, in the present study, *ZBP1* was found to be negatively correlated with CD8 T cell infiltration.

Macrophage cells are critical cells in the inflammation

process and autoimmune disease. Macrophages are tissue resident immune cells that can as immune respond cell. Macrophages canactivated via IgG IC, induce the production of cytokines, such as IL-6, TNFα, IL-1β, and inflammatory mediators (40-42). Jing *et al.* revealed that macrophages may be reprogrammed as therapy targets for LN (43). The biological function of monocytes in SLE has also been explored. Monocyte cells can induce change via cytokines and have a significant effect on SLE (44). Additionally, $CD4^+$ T cells, B cells, and plasma cells also have a strong effect on the progression of SLE (45-47). These results showed that *ZBP1* can play a significant role by regulating various immune cell infiltration in SLE patients.

Conclusions

In the present study, we found that the pyroptosis gene, *ZBP1*, may act as a biomarker for diagnosing and assessing the activity of SLE. Our findings may lead to the development of complementary therapy methods for SLE via the regulation of pyroptosis genes, such as *ZBP1*.

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Footnote

Reporting Checklist: The authors have completed the STREGA reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-6193

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-6193). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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