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ORIGINAL ARTICLE

Microarray expression profile of circular RNAs and mRNAs in children with systemic lupus erythematosus

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Abstract

Background Recently, it was reported that circular RNAs (circRNAs) play the crucial role in many physiological and biological processes and can be used as biomarkers. However, the information about circRNAs in children with systemic lupus erythematosus (SLE) is limited. The aim of this study is to determine the expression of circRNAs in children with SLE and investigate the significance of circRNA for diagnosing SLE.

Methods Microarray profile of circRNAs and mRNAs was performed for identifying the changes in expression of circRNAs and mRNAs between children with SLE and healthy children. Quantitative polymerase chain reaction (qPCR) was used to confirm the results. Spearman correlation test was performed to assess the correlation between circRNAs and clinical variables. The receiver operating characteristic (ROC) curve was calculated for evaluating the diagnostic value.

Results A comparison between the children with SLE and healthy children revealed that 348 circRNAs and 1162 mRNAs were expressed differentially. The authors constructed a complex circRNA target network consisting of 307 matched circRNA-mRNA pairs for 124 differentially expressed circRNAs (74 circRNAs were upregulated, and 50 circRNAs were downregulated) and 142 differentially expressed mRNAs (83 mRNAs were upregulated, and 59 mRNAs were downregulated) by using gene co-expression network analysis. The competing for endogenous RNA (ceRNA) network includes 42 differentially expressed circRNAs, 41 differentially expressed mRNAs, and 71 predicted miRNAs. Among these SLE patients, we detected that the hsa_circ_0021372 and hsa_circ_0075699 levels are associated with C3 and C4 levels in children with SLE. The hsa_circ_0057762 level is positively associated with the SLEDAI-2K score. The ROC curves of circRNAs showed that the levels of hsa_circ_0057762 (AUC 0.804, 95% CI 0.607–1.0, $P = 0.02$) and hsa_circ_0003090 (AUC 0.848, 95% CI 0.688–1.0, $P = 0.008$) could differentiate the patients with SLE from the healthy controls.

Conclusions We firstly characterized the expression profiles of circRNA and mRNA in children with SLE and propose herein their possible roles in the pathogenesis of SLE. These results provide novel insight into the mechanisms of SLE pathogenesis, and circRNAs may serve as useful biomarkers for SLE.

Keywords Children · circRNA · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease [1]. SLE is a disease which is primarily caused by autoantibody production and immune complex deposition. A lot of work has been made to explain the pathogenesis of SLE, but the exact etiology of SLE is still unknown.

At least 90% of the genome is actively transcribed into noncoding RNAs (ncRNAs), which have no protein coding ability. Noncoding RNAs which include microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) play an important role in the pathogenesis of SLE. Several studies have revealed the potential role of miRNAs and lncRNAs in the pathogenesis of SLE and their role as biomarkers for the diagnosis of SLE [2, 3]. Recent evidence has demonstrated that circular RNAs

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(circRNAs) can regulate gene expression and participate in regulation of in healthy and diseased conditions [4].

Studies have demonstrated that circRNAs are involved in the development of several diseases, such as cancer [5], Alzheimer's disease [6], atherosclerotic vascular disease [7], and SLE of adults [8–10]. However, the expression and role of circRNAs in children with SLE is mostly unknown.

circRNAs were recently discovered as a special novel type of endogenous noncoding RNA. They form a covalently closed continuous loop without 5′caps and 3′tails, which makes them resistant to RNase R activity and more stable than linear RNAs [11]. These features indicate that circRNAs may be more suitable biomarkers than other types of RNAs [12]. circRNA was firstly found in RNA viruses in the early 1970s [13]. It was thought that they are molecular flukes or artifacts of aberrant RNA splicing without any functions [14]. Only recently, with the rapid development of high-throughput RNA sequencing (RNA-Seq) technology and bioinformatics method, circRNAs are more and more extensively investigated and their important roles as miRNA sponges [15–17], gene transcription and expression regulators [17, 18], and RNA-binding protein (RBP) sponges [19–21] were discovered. No matter that our knowledge about circRNAs is quite limited, in the past few years, researchers have discovered that some microRNAs are associated with SLE [22, 23], and circRNAs can function as miRNA sponges. It means that circRNAs may have an important role in the pathogenesis of SLE. That is why we aimed to determine the circRNA expression profile in a whole blood from the children with SLE. This study will lay the foundation for the further investigation of the role of circRNA in SLE.

Materials and methods

Patients and specimens

All samples from patients with SLE were obtained from the Department of Rheumatology of Beijing Children's Hospital (Beijing, China). All patients with SLE fulfilled at least four of the revised criteria for SLE by the American College of Rheumatology (ACR). The control group included healthy volunteers with no history of autoimmune disease or immunosuppressive therapy. Four children (age range 7–11 years) first diagnosed with untreated SLE, and four "control" children (age range 8–12 years) were used for microarray analysis. Twenty patients (age range 7–12 years) and 20 control children (age range 8–13 years) were used to validate the microarray results by RT-quantitative polymerase chain reaction (qPCR). Peripheral blood samples (4 ml) were obtained from each patient. The samples were collected in tubes containing ethylenediaminetetra acetic acid (EDTA). After collection, the samples were transferred immediately into liquid nitrogen and stored in a freezer at − 80 °C until RNA extraction.

All participants were taken from the Han Chinese population. The study was approved by the Research Ethics Board of Beijing Children's Hospital, Capital Medical University, China. Informed consent was obtained from all study participants.

Total RNA extraction and microarray analysis

Total RNA was extracted from whole blood by using Trizol Reagent (Life Technologies, CA, USA) and then purified with an miRNeasy Serum/Plasma Kit (Qiagen, Hilden, Germany). RNA was detected by using an UV-vis spectrophotometer (Thermo, NanoDrop 2000, USA) at 260-nm absorbance, and purity and integrity were assessed by agarose gel electrophoresis. The minimum RNA concentration for the microarray was 20 ng/μl. Two hundred fifty nanogram total RNA was used to prepare biotinylated cDNA according to the standard Affymetrix protocol. Following labeling, cDNA was hybridized on a GeneChip® Human Clariom™ D Assay. GeneChips were washed and stained in the Affymetrix Fluidics Station 450. GeneChips were scanned by using an Affymetrix® GeneChip Command Console installed in the GeneChip® Scanner 3000 7G. Data were analyzed by using the robust multichip analysis (RMA) algorithm with Affymetrix default analysis settings. The presented values were log2 RMA signal intensity. Differentially expressed genes between two groups were filtered with criteria $P < 0.05$, fold change > 1.2.

Quantitative polymerase chain reaction analysis

Total RNA was extracted from the peripheral blood by using a Trizol reagent (Life Technologies) following purification with an RNeasy kit (Qiagen, Valencia, CA, USA) according to the manufacturer instructions. M-MLV reverse transcription (Promega) was used to synthesize cDNA. Quantitative PCR analysis and data collection were performed on the ABI 7900HT qPCR system using the primer pairs listed below (Table 1). β-Actin and GAPDH were used as an internal control of circRNA and messenger RNA (mRNA), respectively. Fold changes were shown as mean ± SD in three independent experiments for each triplicate.

Cluster

The Hierarchical Clustering tab allows you to perform hierarchical clustering on your data. This is a powerful and useful method for analyzing all sorts of large genomic datasets. Many published applications of this analysis are given in the references. Cluster currently performs four types of binary, agglomerative, hierarchical clustering. The basic idea is to

Table 1 Primers used for RT-qPCR validation[24–27]

Name	Sequence
hsa_circ_0021372_F	CCTCTGCCCTGGTCGCATAA
hsa_circ_0021372_R	CAGGAAGATCAGGAGCAAGTCC
hsa_circ_0057762_F	GAATTAGCCAGTGGGCAGGT
hsa_circ_0057762_R	TGTGTTCTTGAAGTGCAGAAGC
hsa_circ_0075699_F	TACTTGAATTTCCGGCGGGG
hsa_circ_0075699_R	GGATACCTGTCACTGCTCCG
hsa_circ_0003090_F	TGGTTTCCACAACAACGACAC
hsa_circ_0003090_R	CAGGCACTGTTCTTCAGGGC
ERP27_F	CCTCCACATGGTGACAGAGTACAAC
ERP27_R	GCTTGGCTGCCTTCTGGTATCTG
KLF12_F	AGTATCTTCAGCGTCATCTTCGTCAAC
KLF12_R	AGGCACCGACTGTACCACCAC
TRAF5_F	GAACACCTGGCTGTATGTCCTGAAG
TRAF5_R	GTAAGGCTGAATGCTCATGTTGCTG
RPL9_F	GGCTTCCGTTACAAGATGAGGTCTG
RPL9_R	ATACTGAACAAGCAACACCTGGTCTC
GAPDH_F	GGGAAACTGTGGCGTGAT
GAPDH_R	GAGTGGGTGTCGCTGTTGA
β-actin_F	GTGGCCGAGGACTTTGATTG
β-actin_R	CCTGTAACAACGCATCTCATATT

assemble a set of items (genes or arrays) into a tree, where items are joined by very short branches if they are very similar to each other and by increasingly longer branches as their similarity decreases. The first step in hierarchical clustering is to calculate the distance matrix between the gene expression data. Once this matrix of distances is computed, the clustering begins. Agglomerative hierarchical processing consists of repeated cycles where the two closest remaining items (those with the smallest distance) are joined by a node/branch of a tree, with the length of the branch set to the distance between the joined items. The two joined items are removed from list of items being processed and replaced by an item that represents the new branch. The distances between this new item and all other remaining items are computed, and the process is repeated until only one item remains.

Co-expression network

Compute co-expression coefficient, the expression values of a gene for different samples can be represented as a vector; thus, calculating the co-expression measure between a pair of genes is the same as calculating the selected measure for two vectors of numbers. R function cor.test (test for association/correlation between paired samples) was used to compute the Pearson's correlation coefficient to measure the gene co-expression. Joint differences of circRNA expression spectrum data and the difference of gene expression data to build a circRNA network with the correlation coefficient of gene expression. In the hierarchy to express network clearly reflecting lcircRNA and the mutual relationship between genes and the overall relationship, it further found the circRNA of gene regulation relationships, and explore its possible functions.

Competing for endogenous RNA network

RNA transcripts could combine with common miRNAs; the basis of combining miRNAs is the interaction of its response element (usually 3′ UTR), by predicting these miRNA response components and computing free energy; it can find the competition relationship between RNA transcript in the process of combining, thus discovering these competing for endogenous RNA (ceRNA) biology functions. The following are ceRNA network build-specific steps: (1) Through miRNA-mRNA, circRNA-miRNA target prediction database computation, estimate its target relationship. (2) Compute person coefficient between circRNA and mRNA through their gene expression value. (3) Combined with step 2, find the co-expression between mRNA and circRNA, find the miRNA-mRNA into negative correlation, the circRNA-miRNA into negative correlation of step 1, and at the same time, the miRNA can combine with the relationship between mRNA-circRNA, and the mRNA-circRNA can be ceRNA.

Statistical analysis

All statistical analyses in this study were performed by the Statistical Product and Service Solutions (SPSS) 16.0 software package (IBM, Chicago, IL) and GraphPadPrism 6.0 (GraphPad Software, La Jolla, CA). Associations between parameters were analyzed using the Spearman rank correlation. The clinical diagnostic value of a given circRNA was verified by ROC curve analysis. $P < 0.05$ was considered as statistically significant.

Results

Analysis of differentially expressed circRNAs and mRNAs in peripheral blood from children with SLE

We performed circRNA microarray analysis of the peripheral blood for four children with SLE and for four age- and sex-matched healthy controls to identify differentially expressed circRNAs in SLE children. In order to investigate the potential functions of circRNA, we also performed mRNA microarray analysis. Hierarchical clustering revealed systematic variations between two groups in the expression of circRNAs (Fig. 1) and mRNAs (Fig. 2). In total, 348 circRNAs and 1162 mRNAs were identified as significantly differentially

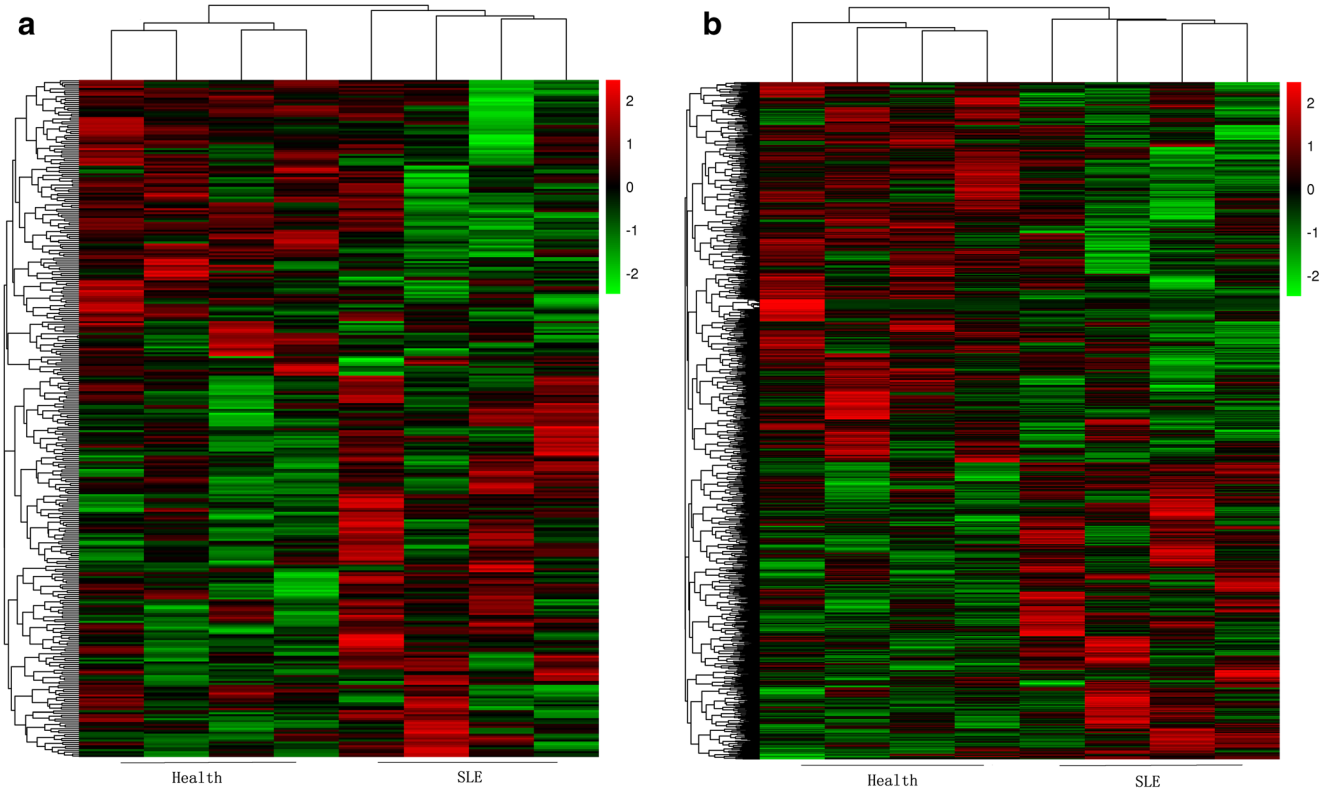

Fig. 1 Hierarchical clustering of circRNAs (**a**) and mRNAs (**b**) in SLE and healthy patients. Red and green colors indicate upregulation and downregulation, respectively

expressed. Compared to the normal children, 184 circRNAs and 501 mRNAs were observed to be upregulated, while 164 circRNAs and 661 mRNAs were downregulated in SLE patients. And the microarray data has been uploaded into a public database (accession number GES110396).

1. Co-expression network

In order to reveal possible modulating mechanisms of the circRNAs, gene co-expression network analysis was constructed. This procedure resulted in a complex circRNA target network that consisted of 307 matched circRNA-mRNA pairs for 124 differentially expressed circRNAs (74 circRNAs were upregulated, and 50 circRNAs were downregulated) and 142 differentially expressed mRNAs (83 mRNAs were upregulated, and 59 mRNAs were downregulated). Within the network, from one to six circRNAs could target a single mRNA.

2. The quantitative RT-PCR validation of differentially expressed circRNAs and mRNA

In order to verify the microarray data, a sample of four circRNAs (hsa_circ_0021372, hsa_circ_0057762, hsa_circ_0075699, and hsa_circ_0003090) and four mRNAs (ERP27, KLF12, TRAF5, and RPL9) was chosen based on the fold changes (≥ 2.0) and significance (P values ≤ 0.01) from the microarray data. We used qRT-PCR to validate the expression level of these differentially expressed circRNAs and mRNAs by using an independent set of samples from 20 SLE children and 20 healthy controls (Fig. 3). The expression tendency of these transcripts was similar to those from microarray data, except hsa_circ_0057762.

3. Prediction of interactions between circRNAs and miRNAs

In order to analyze the functions of the circRNAs, we investigated potential miRNA bonds with circRNAs ($FC > 2$, $P < 0.05$) based on TargetScan and miRanda. Within the network, from 3 to 77 miRNAs could target a single circRNA. Forty-six differentially expressed circRNAs and predicted miRNAs were used to construct the circRNA-miRNA network (Fig. 4).

4. The ceRNA network

Because circRNA can serve as competing for endogenous RNA (ceRNA) in miRNA, we predicted the potential interactions between circRNAs, miRNAs, and mRNAs. Forty-two differentially expressed circRNAs, 41differentially expressed mRNAs, and 71 predicted miRNAs were used for the construction of the ceRNA network (Fig. 5).

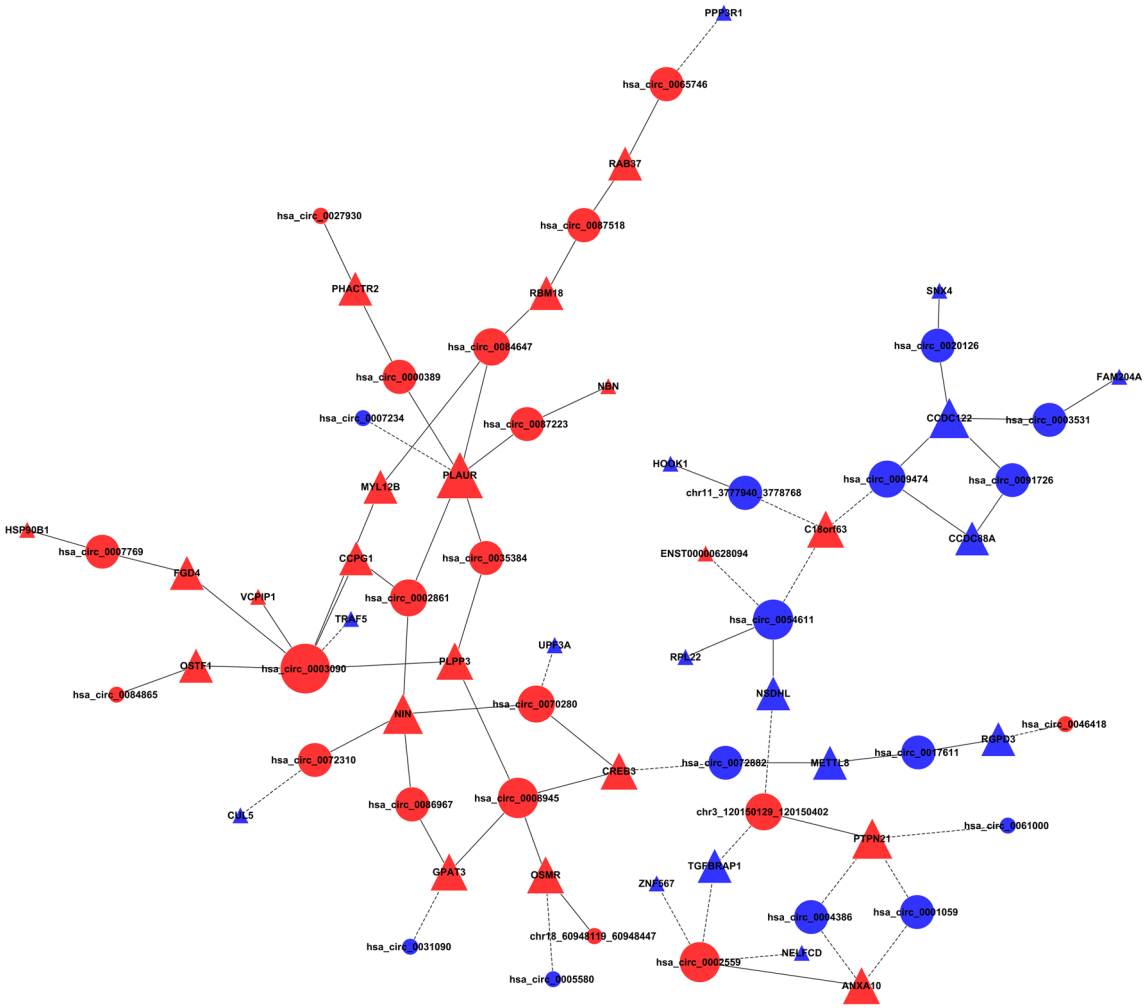

Fig. 2 The circRNA-mRNA co-expression network: Blue color represents the downregulation, and red color represents upregulation. The circles represent circRNAs. The triangles represent mRNAs. The straight line represents the possible relationship, while the dotted line represents the inhibitive effect

5. Association of confirmed circRNA levels with SLE clinical characteristics

To determine whether the significantly and differentially expressed circRNAs in the children with SLE were relevant biomarkers for the activity of disease of SLE, we performed the Spearman correlation test to assess the correlation between SLE-related clinical features (ESR, C3, C4, SLEDAI-2K) and circRNA levels (hsa_circ_0021372, hsa_circ_0057762, hsa_circ_0075699, and hsa_circ_0003090). The hsa_circ_0021372 and the hsa_circ_0075699 levels were associated with C3 and C4 levels in children with SLE. The hsa_circ_0057762 level was positively associated with the SLEDAI-2K score. There is no correlation between hsa_circ_0003090 with ESR, C3, C4, and SLEDAI-2K.

6. The ROC curve analysis of circRNAs among children with SLE

In order to assess the potential value of significantly and differentially expressed circRNAs for SLE diagnosis, we have performed ROC curve analysis (Fig. 6). The ROC curves of circRNAs indicated that the level of hsa_circ_0057762 (AUC 0.804, 95% CI 0.607–1.0, $P = 0.02$) and hsa_circ_0003090 (AUC 0.848, 95% CI 0.688–1.0, $P = 0.008$) could differentiate the patients with SLE from the healthy controls. The hsa_circ_0057762 and hsa_circ_0003090 may be used as the biomarker for SLE diagnosis.

Discussion

SLE is a prototypic autoimmune disease, which is characterized by the production of autoantibodies to various autoantigens, complement consumption, and chronic inflammation [28]. Although genetic, environmental, epigenetic, and hormonal factors are reported to participate in initiation and progression of SLE, nevertheless the exact pathogenesis of

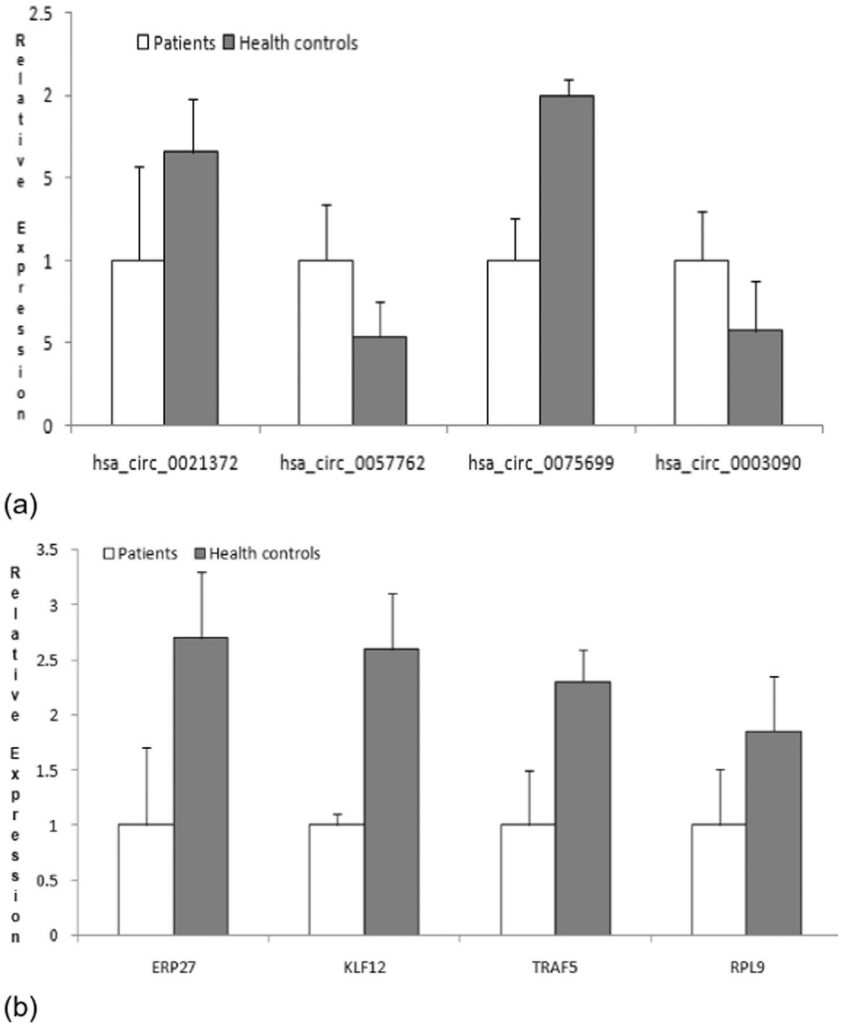

Fig. 3 RT-qPCR validation of selected circRNAs (**a**) and mRNAs (**b**) between children with SLE and healthy children

SLE remains mostly unknown [29]. Numerous studies about gene expression are performed in SLE patients for identification of various differentially expressed genes. In particular, several studies use next-generation sequencing and microarray technologies to globally investigate the transcriptome in monocytes, B cells, T cells, PBMCs, and the whole blood of SLE patients and obtain hundreds or even thousands of dysregulated transcripts including both coding RNAs and ncRNAs [30–32]. Some studies have revealed the potential role of miRNAs and lncRNAs in the pathogenesis of SLE and their role as biomarkers for the diagnosis of SLE [2]. For example, deregulated miRNA expression pattern in the peripheral blood mononuclear cells (PBMCs) from patients with SLE was firstly reported by Dai et al. in 2007. They identified 16 lupus-related miRNAs that were altered specifically in patients with lupus, but not in patients with idiopathic thrombocytopenic purpura [33]. Since then, several reports have been published to demonstrate the dysregulated miRNA expression profiles of PBMC, CD4+ T cells, kidney biopsy, and Epstein-Barr virus (EBV)-transformed B cell lines from the patients with lupus [34–38]. In the study of adult SLE, the linc0949 and linc0597 were significantly decreased in patients with SLE compared with patients with RA and healthy control subjects [39–41]. Other preliminary data in a murine model system pointed to a link between the lncRNA growth arrest-specific 5 (GAS5) and disease susceptibility to SLE [42]. Recent evidence has demonstrated that circRNAs can regulate gene expression and broadly participate in regulation of healthy and diseased conditions. Recently, few studies showed differentially expressed circRNAs in plasma of adult patients with SLE [8–10]. However, the expression and role of circRNAs in SLE is mostly unknown. In this study was reported about the expression of circRNAs in children with SLE and their potential to become a biomarker.

The circRNAs are more stable in mammalian cells compared to miRNAs and lncRNAs [43]. These features provide circRNAs the potential of being the ideal biomarkers for human diseases. Recent studies have revealed that circRNAs can be used as diagnostic or predictive biomarkers for some cancers [44–47], rheumatoid arthritis [48], and for primary biliary cholangitis [49]. For example, the hsa_circ_0001649 has the downregulated expression in hepatocellular carcinoma, and

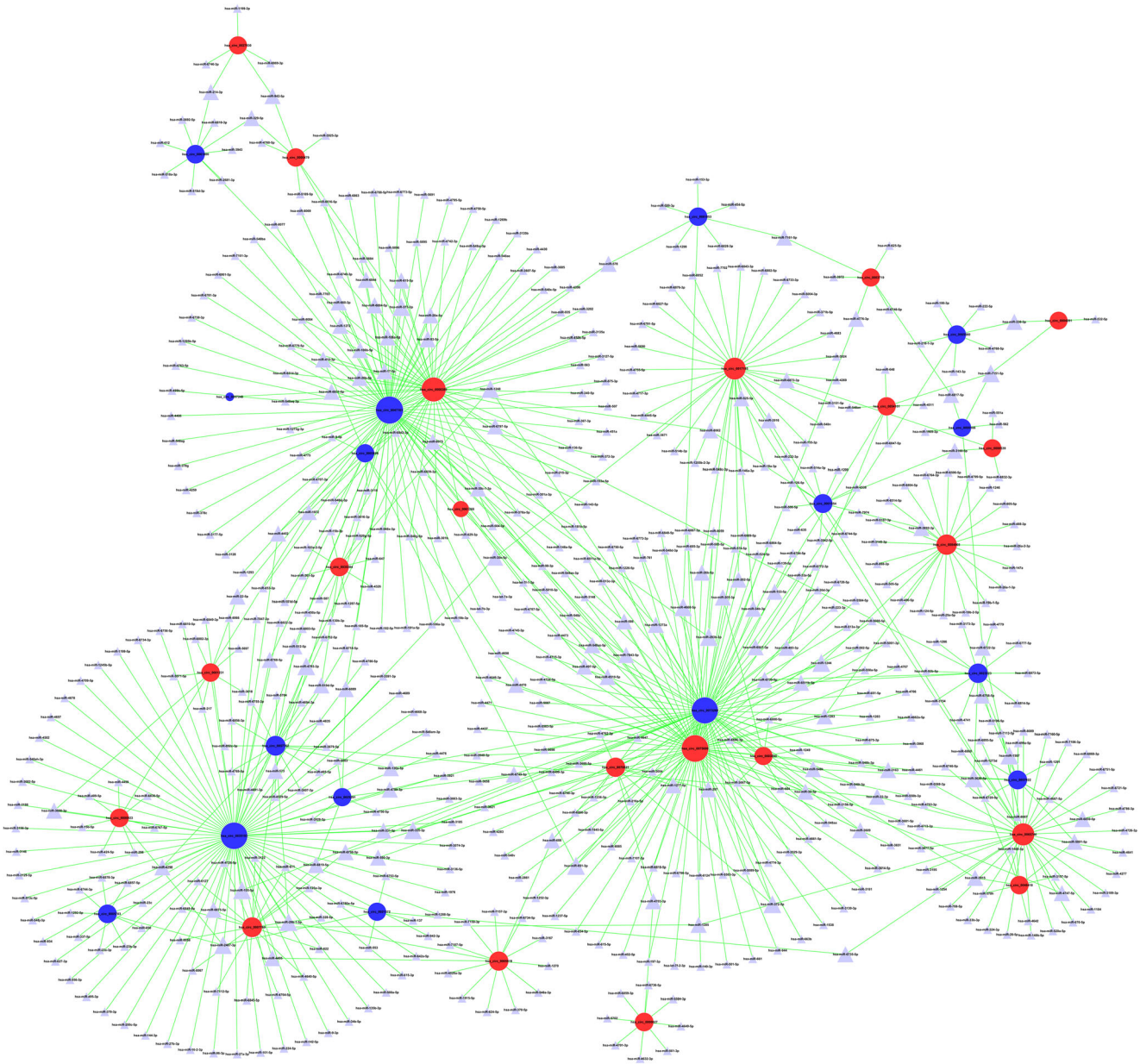

Fig. 4 The circRNA-miRNA network of 46 differentially expressed circRNAs and predicted miRNAs. The blue color represents downregulation, and red color represents upregulation

the sensitivity and specificity for the diagnosis were 81% and 69%, respectively. So, hsa_circ_0001649 could be a new diagnostic biomarker for hepatocellular carcinoma [50]. The hsa_circ_001988 can be used for diagnosis of colon cancer as a biomarker and as a new potential therapeutic target, and the AUC of hsa_circ_001988 is 0.788 [51]. In the study about rheumatoid arthritis, the circRNA_104871 has the significant value for RA diagnosis (AUC = 0.833, $P < 0.001$) [48]. In the studies of SLE, Li et al. demonstrated dysregulated circRNAs in T cells from adult with SLE and revealed the function of hsa_circ_0045272 in negatively regulating apoptosis and interleukin-2 secretion [8]. Zhang et al. illustrated that hsa_circRNA_407176 and hsa_circRNA_001308 in plasma and PBMCs could be potential biomarkers for SLE of adult [10]. Ouyang et al. suggests that upregulated plasma circRNA_002453 level in LN patients was associated with the severity of renal involvement and might also serve as a potential biomarker for lupus nephritis patient diagnosis [52].

In this study, we performed circRNA microarray analysis by comparing the transcript profiles of children with SLE and the healthy controls. A total of 348 significantly and differentially expressed circRNAs were detected, with 184 circRNAs upregulated and 164 downregulated. These investigations may serve for future pathophysiological researches for SLE and help to determine whether circRNAs could be used as a new, noninvasive biomarker for SLE diagnosis and for

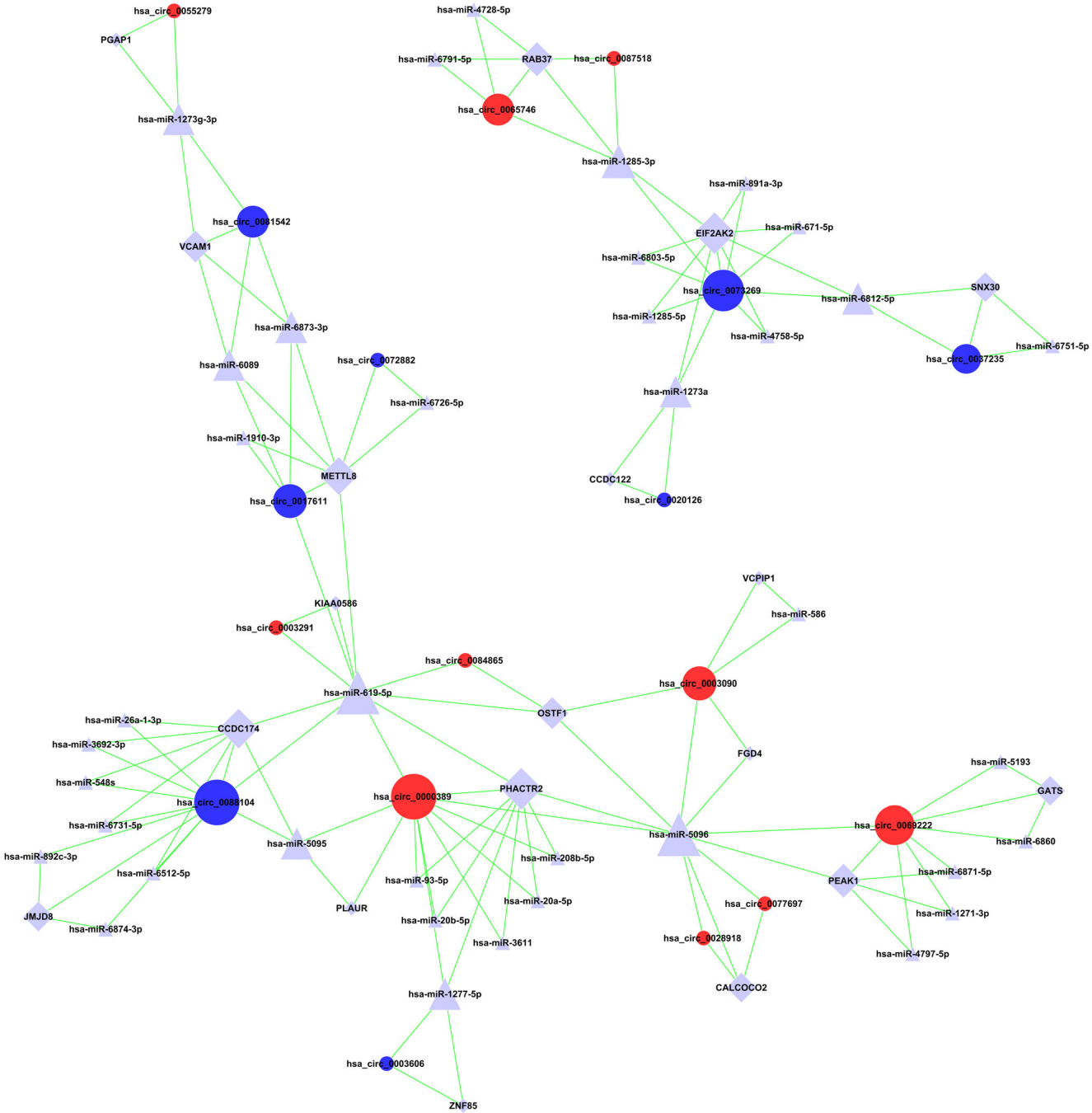

Fig. 5 The circRNA-miRNA-mRNA network. Blue color represents downregulation, and red color represents upregulation

treatment. In this study, we performed ROC curve analysis. The levels of the hsa_circ_0057762 and hsa_circ_0003090 could differentiate the patients with SLE from the healthy controls. Furthermore, in our study was found that the expression of some circRNAs in SLE patients is correlated with C3, C4, and SLEDAI-2K. This means that these circRNAs may be used as relevant biomarkers of disease severity or systemic inflammation in SLE patients. Our results of circRNA microarray screening are different from other studies. The reasons may be as follows: (1) The patients we studied were children, whereas the previous study involved adults. (2) We analyzed circRNA expression in the whole blood of children, whereas the previous study analyzed peripheral blood mononuclear cells or plasma.

In order to reveal possible modulating mechanisms of the circRNAs, the gene co-expression network analysis was constructed. The gene co-expression network includes 817 matched circRNA-mRNA pairs of 124 differentially expressed circRNAs and 142 differentially expressed mRNAs. These results indicate that the altered expression of

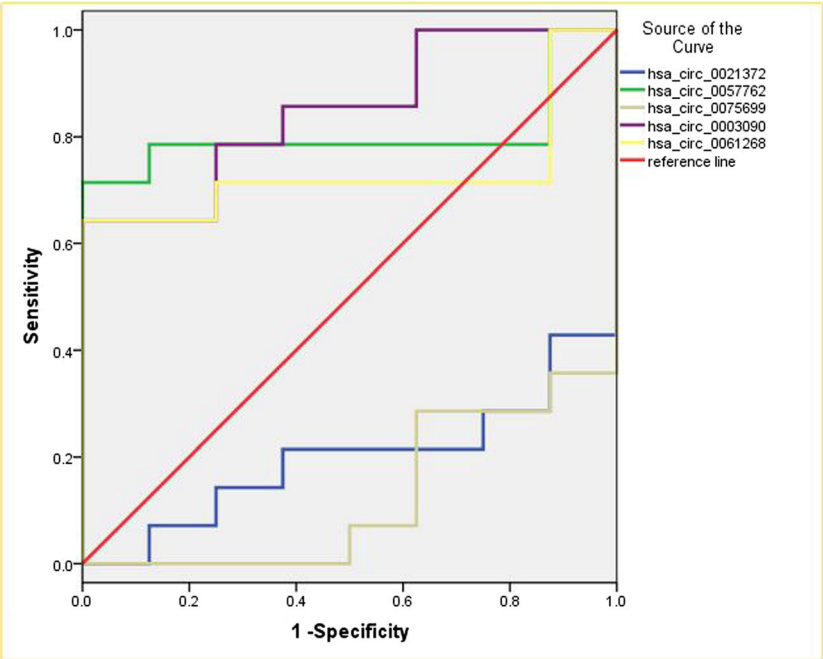

Fig. 6 The ROC curve analyses of circRNAs for diagnosing SLE

Variable	AUC	SEM	p value	95% CI	
				Lower Bound	Upper Bound
hsa_circ_0021372	.196	.094	.020	.012	.381
hsa_circ_0057762	.804	.100	.020	.607	1.000
hsa_circ_0075699	.125	.074	.004	.000	.271
hsa_circ_0003090	.848	.082	.008	.688	1.000
hsa_circ_0061268	.732	.112	.076	.513	.951

circRNAs may be related to their involvement in the pathogenesis of SLE.

In 2011, ceRNA was proposed by Leonardo Salmena et al. It is hypothesized how protein-coding messenger RNAs and noncoding RNAs interact and regulate each other by using miRNA response elements (MREs) as a new communication tool and their competition for binding to common miRNAs. They proposed that ceRNAs participate in posttranscriptional regulation with the help of sponge miRNAs and affect the distribution of miRNAs on their targets [53]. Noncoding RNA IPS1 in *Arabidopsis thaliana* is the first example of endogenous ceRNA sponge miR-399 that antagonizes the effect of miR-399 on the target PHO2 mRNA [54]. Because of the development of bioinformatics, we can predict the possible ceRNA. The ceRNA is also one of circRNA functional mechanism. Therefore, dissecting of ceRNA crosstalk in SLE may help to clarify functions of circRNA. In this study, we constructed ceRNA network by combining circRNA with mRNA by using Chip result and biological information prediction technology. The network revealed that one circRNA can participate in multiple ceRNA networks. It is indicated that circRNA participates in the pathogenic process of SLE through various pathways. Surely, this is only a prediction data, and further studies are needed to confirm this.

In this study, four mRNAs were observed to be downregulated in SLE patients. Tumor necrosis factor receptor (TNFR)-associated factor 5 (TRAF5) was initially identified by two separate groups as a putative signal transducer for CD40 and LTβR, positively regulating activation of the canonical NF-κB pathway. Additionally, TRAF5 has been implicated in activation of the noncanonical NF-κB pathway, JNK, and IRF3/IRF7. Recent studies have demonstrated that TRAF proteins can function in both cell type- and receptor-specific fashions [54]. Endoplasmic reticulum protein 27 (ERp27) is a new human protein disulfide isomerase (PDI) family member. ERp27 contains two domains that are homologous to the noncatalytic b and b′ domains of human PDI, and both probably have a thioredoxin fold. The exact physiological function is unclear [54]. Krüppel-like factor 12 (KLF12) is well known as a repressor of the transcription factor AP-2a. KLF12 is mainly related to tumors such as salivary gland and gastric tumors and is also related to head, neck, and stomach cancers. In addition, the postnatal expression of KLF12 plays an important role in the inner medullary collecting ducts (IMCDs) of kidneys [54]. Ribosomal protein L9 (RPL9) is a component of the 60S subunit that belongs to the L6P family of ribosomal proteins. RPL9 was identified as a Bax suppressor that promotes cell survival in yeast and is overexpressed in colorectal cancer

[54]. The role of these mRNAs in the pathogenesis of SLE is unclear and requires further investigation.

This study has some limitations. Firstly, the sample size is relatively small; the large-sized studies which include people of different races and from different regions are needed to confirm the result. Secondly, determine whether circRNAs could be used as good biomarker for SLE diagnosis and evaluate their ability to effectively differentiate SLE from other rheumatic diseases, infectious diseases, and tumors. Thirdly, the part of the result in this study was obtained through biological information analysis, so further studies are needed to verify the results.

In summary, to the best of our knowledge, this study is the first one which screens and analyzes circRNA expression profiles in children with SLE. This may offer the new insights into the pathogenesis of SLE and may be a promising method of investigation of the molecular pathogenesis of SLE. In addition, we have found that circRNAs may be used for SLE diagnosis and for monitoring the disease activity. Further investigations are required for interpreting the functional mechanism of circRNA and for determining the extent of their serving as a novel therapeutic target and as the diagnostic biomarker for SLE.

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Compliance with ethical standards

Disclosures None.

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