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Characterization of miRNA-mRNA-Pathway Network Predicts Significant Biomarkers for Renal Injury in Kidney Biopsies from Patients with Lupus Nephritis

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ABSTRACT In this study, a miRNA-mRNA-pathway network (MMPN) was proposed to identify the predictive biomarkers for response to immune-suppression drugs in the treatment of lupus nephritis (LN). The steps were: detecting differentially expressed genes and differential pathways, predicting miRNAs by computing targetScores, MMPN construction and topological properties for MMPN. Overall, 43 and 37 differential pathways were respectively identified in 3 months (experiment 1 group) and 6 months (experiment 2 group). The most significant common pathway was ribosome. In the MMPN for experiment 1 group, ribosome pathway was regulated by hsa-miRNA-34c. In the MMPN for experiment 2 group, ribosome pathway was regulated by hsa-miRNA-23b, hsa-miRNA-9-3p, hsa-miRNA-530f, and hsa-miRNA-449b. Based on the degree > 30, 6 nodes were extracted as hubs in experiment 1 and 2 groups, including hsa-let-7f, hsa-miRNA-147, hsa-miRNA-34c, hsa-miRNA-146b, ribosome pathway, and hsa-miR-530f. Ribosome, hsa-miRNA-34c, hsa-miRNA-530f, might serve as prognostic biomarkers of LN outcomes and treatment response.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic and chronic inflammatory disease, which is characterized by producing autoantibodies against a series of self-antigens and inducing damage to any organ system, for example, joints, skin, and the central nervous system (Sanz 2014). Lupus nephritis (LN), kidney involvement in SLE patients, is a common and severe complication of SLE. LN is frequently related to a poor prognosis as well as remains a leading cause of end-stage renal disorders, linked to a higher than fourfold increase in mortality of SLE patients (Bernatsky et al. 2006). LN continues to be one of the most clinical manifestations of SLE (Gurevitz et al. 2013). Throughout the years, immunosuppression treatment is effective to control LN and has improved disease outcomes. Unfortunately, approximately 20 percent of patients with severe LN will progress to refractory LN (Ginzler et al. 2005). Moreover, there are many adverse effects in the process of immunosuppression therapy including malignancy, infection, and metabolic disturbances. Currently, there are no bio-signatures that can reliably determine refractoriness or response to treatment. These adverse effects and high rate of relapse has driven the seek for reliable biomarkers which are able to evaluate disease activity, find patients at risk for kidney damage, and aid early intervention to improve favorable outcomes.

MicroRNAs (miRNAs) are small non-coding RNAs of 22-25 nucleotides, which exert indispensable regulatory functions in regulating gene expression at the posttranscriptional level, thereby affecting stability of transcripts (Thomou et al. 2017). Emerging evidence has demonstrated that miRNAs play a vital role in autoimmunity (Dai and Ahmed 2017), and in LN particularly (Chafin and Reilly 2013). Furthermore, miR-

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NAs are promising biomarkers and are involved in pathogenesis of kidney diseases. A previous study found that hsa-miRNA-638, hsa-miRNA-146a, hsa-miRNA-198 and hsa-miRNA-150 were differentially expressed between LN and normal controls (Lu et al. 2012). Another study has suggested that miRNA-150 promotes renal fibrosis by increasing profibrotic molecules through down-regulating SOCS1 (Zhou et al. 2013). Nevertheless, most of the studies have paid more attention on only one or a few miRNAs or pathways based on the limited samples. Few studies focused on the specific pathways regulated by miRNAs during the development of LN and treatment.

Hence, in this study, with the goal of better predicting the clinical effect of immunosuppression therapy in LN, the researchers planned to identify the risk pathways regulated by LN-related miRNAs via constructing an miRNA-mRNA-pathway network (MMPN). After that, the topological characteristics of the MMPN were measured, and then how the miRNAs regulated those risk pathways was determine. The researchers believe that the molecular information from kidney tissue may be helpful in the prognosis of LN. Aside from that, these identified biomarkers may prove to be beneficial in future targeted therapies and offer insightful information on factors contributing to predicting the response to anti-immune in LN.

METHODOLOGY

The current analysis was comprised of the following steps- microarray data selection, finding differentially expressed genes (DEGs), and significant pathways through Fisher-test based on DEGs using DAVID software, predicting miRNAs according to the DEGs by computing targetScores, MMPN construction and the topological properties for MMPN. The detailed information of each step is described in Figure 1.

Samples

To reveal the molecular mechanisms of immunosuprression therapy in LN, microarray analyses of peripheral blood of patients with LN were performed in 30 females, including 10 control samples (LN patients, before administration of immunosuppressive therapy), 10 patients with nephritis, 3 months after administration of immunosuppressive therapy, and 10 LN patients, 6 months after administration of immunosuppressive therapy. These data were deposited in the E-GEOD-72747 of ArrayExpress database (Abdel-Rahman et al.), based on the platform of A-AFFY-44 - Affymetrix GeneChip Human Genome U133 Plus 2.0 [HG-U133_Plus_2]. The downloaded microarray profile for the 30 samples were further analyzed to identify DEGs.

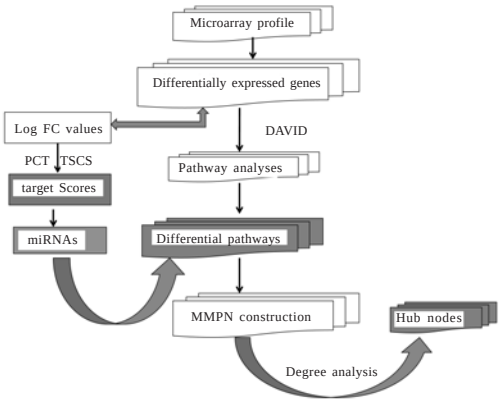

Fig. 1. The flowchart exhibiting the workflow step-by-step
Source: Author

Data Pre-processing and Identification of DEGs

E-GEOD-72747 data included the match-paired specimens (serial whole blood samples from LN patients prior to (control), 3 months (experiment 1), and 6 months (experiment 2) after initiation of conventional immunosuppressive therapy). The immunosuppression drugs included corticosteroids, IV cyclophosphamide and oral mycophenolate. These data were divided into 2 paired groups: control vs. experiment 1, and control vs. experiment 2. Then, the researchers performed differential expression analysis for these two groups.

The platform annotation files provided by Affymetrix were utilized to map the association between probes and gene symbols. Then, quartile data normalization was conducted based on the Affy package (Bolstad et al. 2003) and LIMMA package (Smyth 2005) of R language was employed to compute the expression level of each gene between any two groups to further identify DEGs. After that, the researchers transformed all expression values into to fold-changes (FC) with log2 base (herein, this means log-

FC). The logFC score for each gene was defined as log(control) - log(experiment 1 or 2). Then, the researchers investigated the distribution of the logFC value for each gene. LogFC represents the differential expression degree. Subsequently, multiple test was used to correct the raw P values through Benjamini and Hochberg (Benjamini et al. 2001) method based on false discovery rate (FDR). FDR < 0.05 and |logFC| > 2 were applied as cut off criteria in the DEG identification. After extracting the DEGs in the experiment 1 and experiment 2 groups, experiment 1-specific- and experiment 2 specific and common DEGs between the two groups were screened out.

Pathway Analyses for DEGs

To further reveal the biological roles of DEGs, pathway enrichment analyses for the screened DEGs in the experiment 1 and experiment 2 groups were implemented through the Database for Annotation, Visualization and Integrated Discovery (DAVID, http://david.abcc.ncifcrf.gov/) (Huang et al. 2009) using the Expression Analysis Systematic Explorer (EASE) test (version 2.0, http://david.abcc.ncifcrf.gov/ease/ease.jsp) (Ford et al. 2006). The EASE score was used to select the significant pathway categories. In this study, the pathways with FDR < 0.05 were identified to be differential pathways.

TargetScore Calculation and Prediction of Potential miRNAs

Through the literature, TargetScan context score (TSCS) is a sequence-based value for the single target site, which was calculated based on the method of TargetScan (Garcia et al. 2011). Proabilities of conserved targeting (PCT) is the probability of conserved targeting for individual target site (Friedman et al. 2009). TargetScore package takes logFC and sequence scores as inputs to compute the probability of each gene being the target of a given miRNA. The "TargetScore" provides a convenient and easy way to obtain targetScore with pre-computed input (logFC, TSCS, and PCT), and targetScore ranges from 0 to 1 (Wilson and Keddy 1986). The higher of the targetScore value, the greater of the accuracy in detecting targets. Consequently, using logFC, TSCS, and PCT scores, the researchers calculated the targetScore for the genes involved in the differential pathways to further extract the potential miRNAs using Variational Bayesian-Gaussian Mixture Model (VB-GMM) (Khan et al. 2009). The distribution of targetScore for validated and non-validated targets of all miRNA-mRNA interactions was evaluated. In this paper, the researchers determined the pre-defined ê as the cut-off criteria when little overlap between the two distribution when targetScore = ê existed.

MMPN Construction

Subsequently, according to the target gene sets, the miRNA-regulated pathways were identified. Next, an MMPN consisting of miRNAs, genes, and their common pathways was constructed, which was displayed using Cytoscape 2.8.3. Next, the topological characteristics of the MMPN were measured relying on the Network Analysis plugin (Smoot et al. 2011).

RESULTS

Identifying DEGs

Subsequent to probes mapping to gene symbols, there were the same number of genes (20,514) in the experiment 1 and experiment 2. Then, experiment 1-specific and experiment 2 specific and common DEGs between the two groups were screened out. When the criteria of FDR < 0.05 and |log FC| > 2, there were 103 and 100 DEGs in experiment 1 and experiment 2 groups, respectively. Significantly, a total of 61 common genes in these two groups were extracted. Specific information about DEGs is shown in Table 1. From this table, these DEGs were found to be related to ribosomes. The top 5 significant common DEGs were respectively RPS19, RPL6, RPL35, RPL8, and RPL36.

Identification of Differential Pathways

The enriched significant pathways of DEGs in the experiment 1 and 2 are demonstrated in Table 2. Using the criteria of FDR< 0.05, a total of 43 and 37 pathways were extracted in the experiment 1 and 2 groups, respectively. The relationship between pathways and DEGs in experiment 1 group is shown in Figure 2, and the relationship between pathways and DEGs in experiment 2 group is exhibited in Figure 3. Among these pathways, there were 28 common path-

Table 1: List of experiment 1-specific and experiment 2 specific and common DEGs between the two groups

Experiment 1-specific DEGs	*Experiment 2-specific DEGs*	*Common DEGs*
RPS19	RPS19	RPS19
RPL36	RPL6	RPL6
RPL8	RPL35	RPL35
RPL35	RPL8	RPL8
RPS5	RPL36	RPL36
RPL18	RPS16	RPS16
RPS16	EIF3E	EIF3E
RPL6	RPS5	RPS5
EIF3G	RPL27	RPL27
RPL27	RPL18	RPL18
EIF3D	EIF3K	EIF3K
EIF2S1	EIF3D	EIF3D
SPCS1	SPCS1	SPCS1
EIF3K	RPL19	RPL19
EIF3E	RPL29	RPL29
KIF11	FAU	FAU
NCAPG	RPS24	RPS24
RPL19	NCBP2	NCBP2
RPL29	RPL37	RPL37
RPL12	SEC61G	SEC61G
RPL3	RPS15A	RPS15A
CDC6	RPL12	RPL12
TRAM1	RPS10	RPS10
CCNB1	RPS29	RPS29
RPL22	EIF2S1	EIF2S1
RPS6	EIF4B	EIF4B
RPS3	RPL22	RPL22
RPL37	RPS9	RPS9
NUSAP1	EIF3F	EIF3F
RPLP0	RPLP0	RPLP0
FAU	RPL15	RPL15
SSR1	RPS6	RPS6
DLGAP5	RPL35A	RPL35A
RPS10	RPS23	RPS23
RPL15	EIF3I	EIF3I
NCBP2	RPL11	RPL11
RPS23	RPS3	RPS3
EIF3I	RPL3	RPL3
RPL11	RPL31	RPL31
RPL30	RPL30	RPL30
TTK	RPL34	NCBP1
RPL35A	NCBP1	EIF3H
RPS9	EIF3H	SSR2
RNPS1	SNRPD3	SSR4
RPS15A	SSR2	RPL9
RPL37A	SSR4	EIF3J
EIF3F	RPL9	RPS7
MCM4	EIF3J	RPL24
EIF4B	RPS7	RPL10A
CDCA3	RPL24	RPL32
RPL9	RPL10A	RPL14

ways in these two groups. The top 5 common pathways were ribosome, RNA transport, spliceosome, protein export, and mRNA surveillance pathway, respectively. Moreover, the pathway of ribosome was enriched by the most DEGs.

Table 1: Contd...

Experiment 1-specific DEGs	*Experiment 2-specific DEGs*	*Common DEGs*
EIF3H	RPL32	RPL37A
AURKA	RPL14	RPS14
RPS29	NUP37	RPS4X
SSR4	RPL37A	KIF11
SEC61G	RPS14	EEF2
SSR2	CPSF3	EIF3G
RPS24	UPF3B	SRP72
OIP5	PSMD7	NUSAP1
RRM2	RPS4X	CCNB1
BUB1	SNRPA1	NCAPG
EIF3J	RPS27A	DTL
RPL14	KIF11	
RAD51AP1	RPL7	
SRP72	UPF3A	
RPL32	RPS2	
RPS7	PSMC4	
NCBP1	SNRPF	
MELK	NUP88	
CDCA5	PSMD8	
CDC20	NDUFAB1	
DTL	EEF2	
BUB1B	NUP155	
RPL10A	NUP210	
BIRC5	EIF3G	
SRP19	NDUFB5	
TOP2A	SRP72	
ASPM	NDUFB7	
TYMS	NUSAP1	
EIF5B	SRSF7	
RPL24	CCNB1	
CCNB2	PSMA7	
GSPT2	PSMD11	
CENPF	NUP133	
MND1	ANAPC5	
CDC45	SRSF11	
NEK2	SNRPD2	
KIAA0101	SRP14	
RAD51	RPL39	
EEF2	SNRPA	
SHCBP1	PSMC2	
UBE2C	PSMD12	
TK1	NCAPG	
RPS4X	NFX1	
TPX2	NDUFB2	
NUF2	DTL	
AURKB	NUP85	
RPL31	RFC4	
RPS14	SNRPB2	
HMMR	PSMA4	
MCM2		
KIF15		
HJURP		

DEGs: differentially expressed genes.

Construction of MMPN

The researchers firstly computed the TargetScores using the combination data of logFC, TSCS, and PCT values, and then the research-

ers obtained the distribution of targetScores. Based on the targetScores distribution, when targetScore was 0.4, little overlap between the two distribution was found. Thus, the researchers selected targetScore > 0.4 as the threshold to discard the less confidence miRNAs. Using the targetScore value > 0.4, a total of 103 genes, 83 miRNAs, and 513 miRNA-gene interactions were identified in experiment 1 group. Moreover, there were 99 genes, 90 miRNAs, and 465 miRNA-gene interactions in experiment 2 group.

The researchers then constructed an MMPN for experiment 1 group, which is shown in Figure 4. In this network, the most significant common pathway (ribosome) was regulated by hsa-miRNA-34c. The second common pathway of RNA transport was regulated by 5 miRNAs (hsa-miRNA-146b, hsa-miRNA-30d, hsa-miRNA-530f, hsa-let-7f, and hsa-miRNA-449a).

Further, the researchers also constructed an MMPN for experiment 2 group, which is shown in Figure 5. In this network, the most significant common pathway (ribosome) was regulated by hsa-miRNA-23b, hsa-mi RNA-9-3p, hsa-miRNA-530f, and hsa-miRNA-449b. The second most significant common pathway (RNA transport) was regulated by hsa-miRNA-34c, and hsa-miRNA-9*.

Topological Features of the MRPN to Extract Significant Nodes

In order to identify more important nodes, the researchers measured the topological characteristics of the network (degree distribution). The degree distribution followed a power law distribution using all of the nodes in the MMPN. Based on the degree > 30, a total of 6 nodes as hub nodes in experiment 1 group, including has-let-7f (degree = 55), hsa-miRNA-147 (degree = 54), hsa-miRNA-34c (degree = 45), hsa-miRNA-146b (degree = 43), ribosome pathway (degree = 39), and hsa-miR-530f (degree = 37). In addition, there were also 6 hub nodes, including hsa-miRNA-34c (degree = 50), ribosome pathway (degree = 44), hsa-let-7f (degree = 42), hsa-miR-530f (degree = 37), hsa-miRNA-147 (degree = 36), and hsa-miRNA-146b (degree = 33). From these results, the researchers found that the hub nodes in these two groups were the same. Further, the researchers believe that these hub nodes can reflect the clinical effect of immune-therapy in LN.

DISCUSSION

Corticosteroids as well as cyclophosphamide are the common drugs which are applied to treat LN. Although efficient in preventing renal disease, long-term side effects are common and are associated with the cumulative dose of drugs or the duration of therapy. The discovery of new bio-signatures for LN could help in mitigating the side effects through predicting the severity as well as response of renal flares, thereby allowing for the adjustment of therapeutic schedule with the disease stage. Currently, there are no bio-signatures that can reliably determine refractoriness or response to treatment. In this study, the researchers proposed an MMPN to identify the predictive biomarkers for response to immune-suppression. This work identified 43 and 37 differential pathways in experiment 1 and 2 groups. The most significant common pathway was ribosome. Moreover, the pathway of ribosome was enriched by the most DEGs in the two groups. The MMPN for experiment 1 group demonstrated that the most significant common pathway (ribosome) was regulated by has-miRNA-34c. The second common pathway of RNA transport was regulated by 5 miRNAs, for example, hsa-miRNA-530f. Further, the MMPN for experiment 2 group showed that the most significant common pathway (ribosome) was regulated by hsa-miRNA-23b, hsa-miRNA-9-3p, hsa-miRNA-530f, and hsa-miRNA-449b. The second most significant common pathway (RNA transport) was regulated by hsa-miRNA-34c, and hsa-miRNA-9*. Based on the degree > 30, a total of 6 nodes as hub nodes in experiment 1 and 2 groups, including hsa-let-7f, hsa-miRNA-147, hsa-miRNA-34c, hsa-miRNA-146b, ribosome pathway, and hsa-miR-530f. The researchers believe that these hub nodes, especially, ribosome, hsa-miRNA-34c, hsa-miRNA-530f, can reflect the clinical effect of immune-therapy in LN.

Autoantibodies are believed to be produced via immunological exposure of intracellular proteins and ribosomal P proteins (Fadda et al. 2017). The mammalian phosphoproteins P0, P1 and P2 have been suggested to be related to the 60S ribosomal subunit comprising the stalk structure (Gonzalo et al. 2001) which exerts important functions in the elongation phase of ribosomal protein synthesis. Autoantibodies against the ribosomal P proteins are associated with tissue

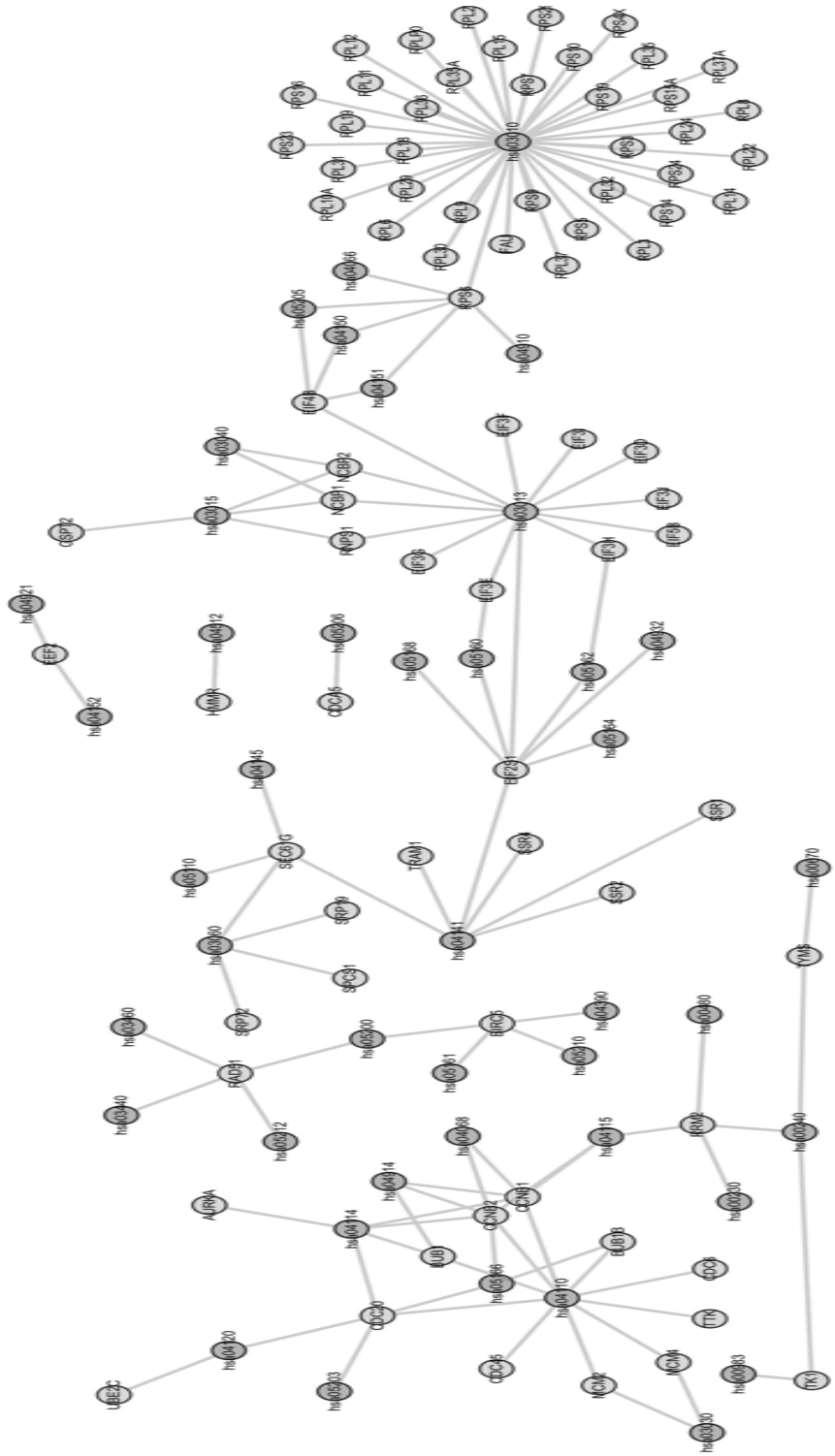

Fig. 2. The relationships of differentially expressed genes (DEGs) and differential pathways in control vs. experiment 1 group. The nodes with hsa(number) stood for pathways, and the other nodes were genes.
Source: Author

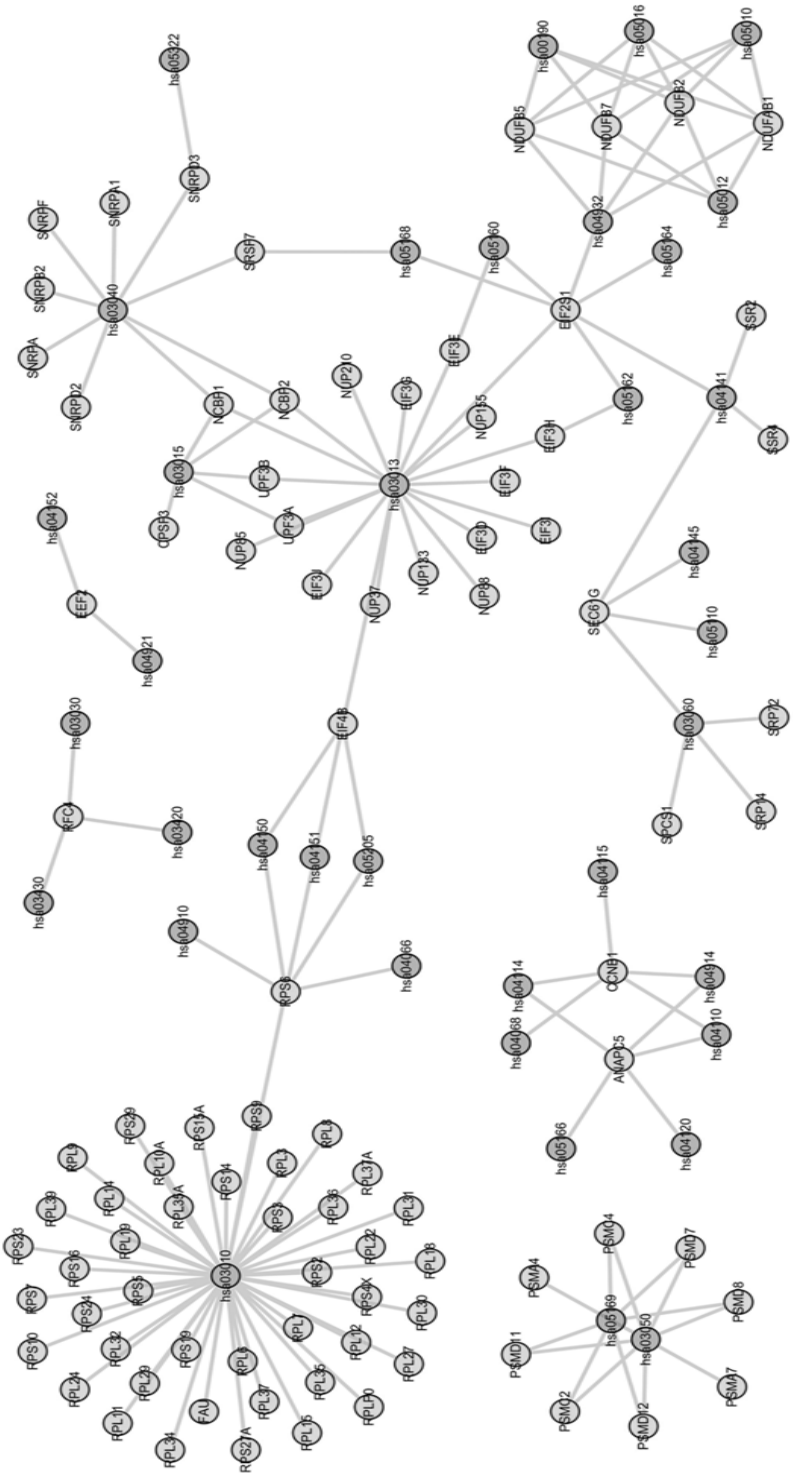

Fig. 3. The relationships of DEGs and differential pathways in control vs. experiment 2 group. The nodes with has(number) stood for pathways, and the other ones were genes.
Source: Author

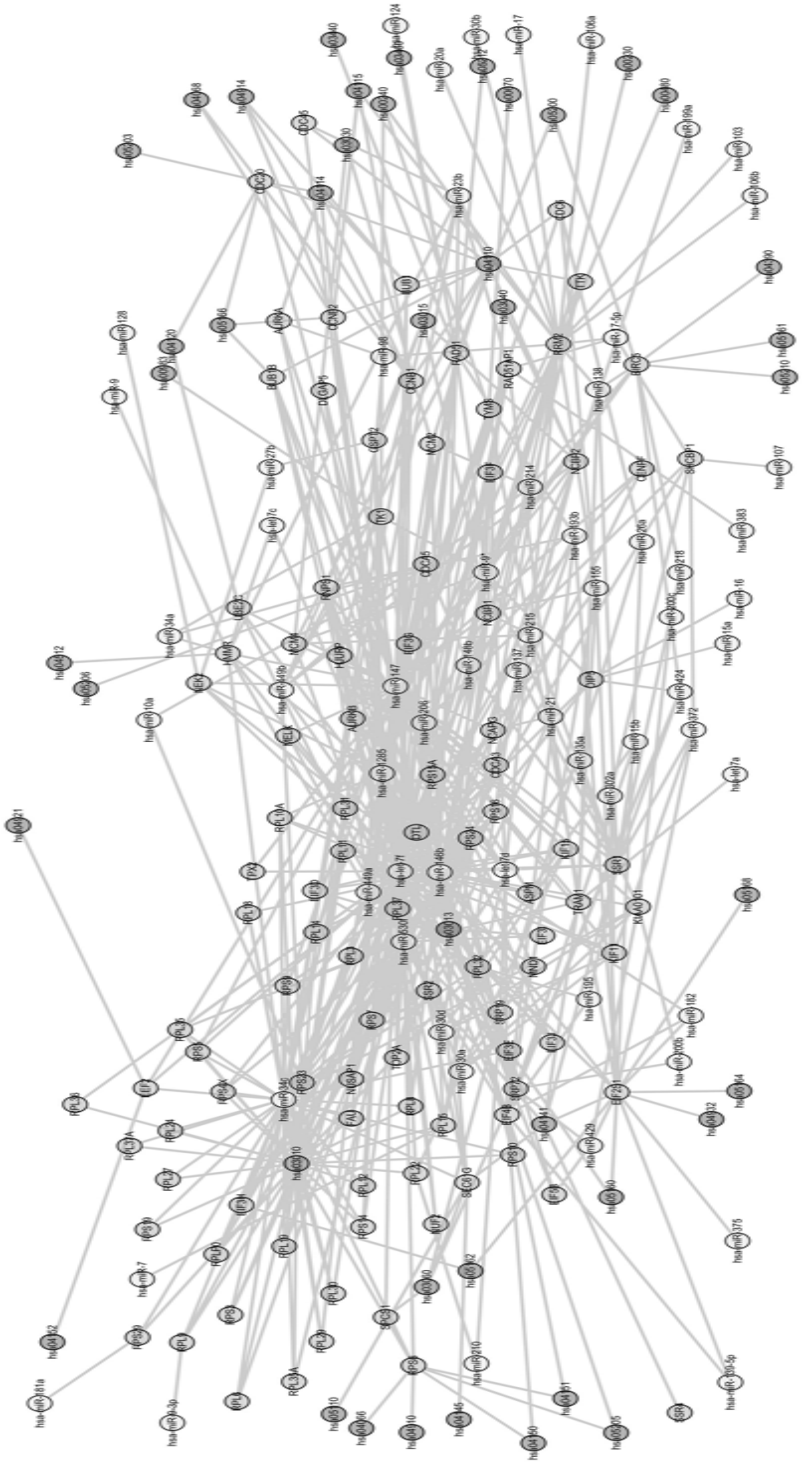

Fig. 4. MiRNA-mRNA pathway network (MMPN) in control vs. experiment 1 group. Network organization of pathway, gene and miRNA interactions. The nodes with has-miR-(number) represented miRNAs, the nodes with has(number) indicated pathways, and the remaining nodes devoted genes
Source: Author

Table 2: Significant pathways enriched by DEGs in experiment 1 and experiment 2 groups

Pathways in experiment 1	*Pathways in experiment 2*
Ribosome [PATH:hsa03010]	Spliceosome [PATH:hsa03040]
RNA transport [PATH:hsa03013]	Protein export [PATH:hsa03060]
Cell cycle [PATH:hsa04110]	mRNA surveillance pathway [PATH:hsa03015]
Protein export [PATH:hsa03060]	Non-alcoholic fatty liver disease (NAFLD) [PATH:hsa04932]
Oocyte meiosis [PATH:hsa04114]	Epstein-Barr virus infection [PATH:hsa05169]
Protein processing in endoplasmic reticulum [PATH:hsa04141]	Oxidative phosphorylation [PATH:hsa00190]
mRNA surveillance pathway [PATH:hsa03015]	Parkinson's disease [PATH:hsa05012]
p53 signaling pathway [PATH:hsa04115]	mTOR signaling pathway [PATH:hsa04150]
DNA replication [PATH:hsa03030]	Protein processing in endoplasmic reticulum [PATH:hsa04141]
Progesterone-mediated oocyte maturation [PATH:hsa04914]	Mismatch repair [PATH:hsa03430]
Pyrimidine metabolism [PATH:hsa00240]	PI3K-Akt signaling pathway [PATH:hsa04151]
mTOR signaling pathway [PATH:hsa04150]	Progesterone-mediated oocyte maturation [PATH:hsa04914]
One carbon pool by folate [PATH:hsa00670]	Alzheimer's disease [PATH:hsa05010]
MicroRNAs in cancer [PATH:hsa05206]	Huntington's disease [PATH:hsa05016]
Homologous recombination [PATH:hsa03440]	HTLV-I infection [PATH:hsa05166]
Pathways in cancer [PATH:hsa05200]	DNA replication [PATH:hsa03030]
Drug metabolism - other enzymes [PATH:hsa00983]	Nucleotide excision repair [PATH:hsa03420]
PI3K-Akt signaling pathway [PATH:hsa04151]	Vibrio cholerae infection [PATH:hsa05110]
Glutathione metabolism [PATH:hsa00480]	Phagosome [PATH:hsa04145]
Fanconi anemia pathway [PATH:hsa03460]	Cell cycle [PATH:hsa04110]
Vibrio cholerae infection [PATH:hsa05110]	Oocyte meiosis [PATH:hsa04114]
Colorectal cancer [PATH:hsa05210]	p53 signaling pathway [PATH:hsa04115]
Viral carcinogenesis [PATH:hsa05203]	Oxytocin signaling pathway [PATH:hsa04921]
Pancreatic cancer [PATH:hsa05212]	Measles [PATH:hsa05162]
Spliceosome [PATH:hsa03040]	Influenza A [PATH:hsa05164]
Hepatitis C [PATH:hsa05160]	Hepatitis C [PATH:hsa05160]
FoxO signaling pathway [PATH:hsa04068]	Ubiquitin mediated proteolysis [PATH:hsa04120]
Measles [PATH:hsa05162]	HIF-1 signaling pathway [PATH:hsa04066]
Ubiquitin mediated proteolysis [PATH:hsa04120]	FoxO signaling pathway [PATH:hsa04068]
Purine metabolism [PATH:hsa00230]	AMPK signaling pathway [PATH:hsa04152]
Influenza A [PATH:hsa05164]	Insulin signaling pathway [PATH:hsa04910]
Herpes simplex infection [PATH:hsa05168]	Proteoglycans in cancer [PATH:hsa05205]
Hippo signaling pathway [PATH:hsa04390]	Systemic lupus erythematosus [PATH:hsa05322]
HIF-1 signaling pathway [PATH:hsa04066]	Herpes simplex infection [PATH:hsa05168]
AMPK signaling pathway [PATH:hsa04152]	Proteasome [PATH:hsa03050]
ECM-receptor interaction [PATH:hsa04512]	RNA transport [PATH:hsa03013]
Phagosome [PATH:hsa04145]	Ribosome [PATH:hsa03010]
Insulin signaling pathway [PATH:hsa04910]	
Oxytocin signaling pathway [PATH:hsa04921]	
Proteoglycans in cancer [PATH:hsa05205]	
Non-alcoholic fatty liver disease (NAFLD) [PATH:hsa04932]	
HTLV-I infection [PATH:hsa05166]	

destruction (Liu and Davidson 2012), and antibodies to ribosomal P proteins have been shown to be more prevalent in patients with LN (Fadda et al. 2017). Thus, measuring the level of ribosome is important for investigating the clinical response of immune-therapy drugs in LN. Of note, hsa-miRNA-34c as a hub node in the MMPN regulated this pathway of ribosome in LN patients 3 months after administration of immunosuppressive therapy in the current work. As the time went on, the pathway of ribosome in LN patients 6 months after administration of immunosuppressive therapy was regulated by hsa-miRNA-530f. Through the literatures, the relationship of hsa-miRNA-34c or hsa-miRNA-530f and ribosome is reported herein for the first time. Based on these results, ribosome pathway here may act as specific signature and could be served as a marker for the evaluation of clinical response to drugs in LN through being regulated by hsa-miRNA-34c and hsa-miRNA-530f at different stages of treatment.

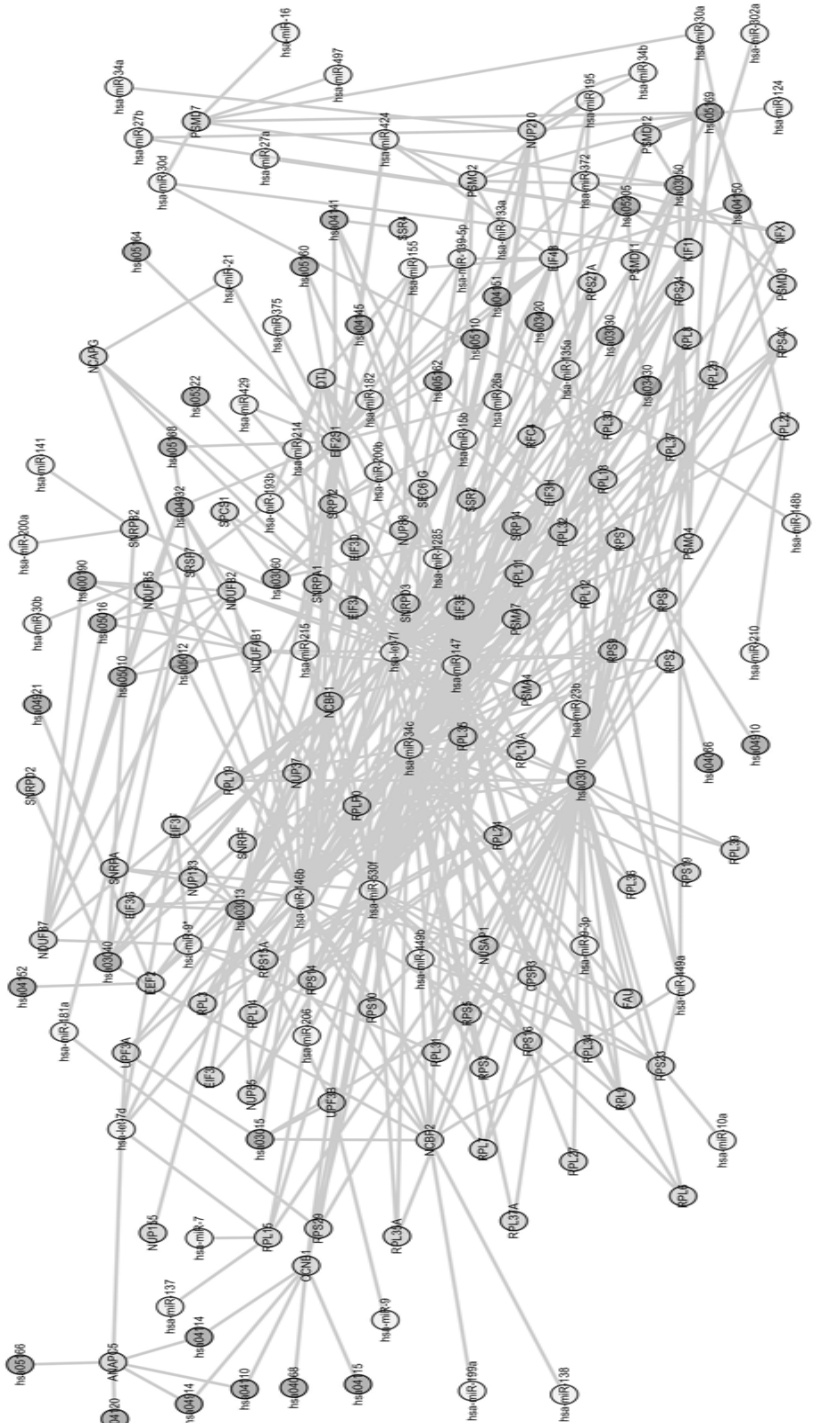

Fig. 5. Deposition of MMPN in control vs. experiment 2 group. Network organization of pathway, gene and miRNA interactions. The nodes with has-miR-(number) represented miRNAs, the nodes with has(number) indicated pathways, and the remaining nodes devoted genes.
Source: Author

Although several important biomarkers were identified, there were some drawbacks in the study. Firstly, sample size was little. Secondly, the microarray profile data were downloaded from the public database, not made by the researchers in the current study. Last but not least, the findings were not verified using animal model or patient tissues. Thus, in the later work, validation experiments using animal or patient tissues will be done to further confirm these findings.

CONCLUSION

Based on the results, differential pathway, ribosome, was successfully identified. Moreover, the pathways-related miRNAs (hsa-miRNA-34c, hsa-miRNA-530f) may be involved in the response to immuno-suppression therapy drugs. These miRNAs and pathways may serve as prognostic biomarkers of renal outcomes and treatment response, which can establish a more personalised management for LN in the future

RECOMMENDATIONS

In the current study, we constructed an MMPN to better investigate the relationship among mRNAs, pathways, and miRNAs and to identify promising biomarkers for LN to predict the clinical response to immune-therapy.

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