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Overproduction of Mitochondrial Fission Proteins and Mitochondrial Fission in Podocytes of Lupus Nephritis Patients

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Background: The glomerular injury is associated with different pathogeneses, and podocyte damage is common in various ISN/RPS class lupus nephritis (LN). In podocyte, mitochondrial morphological changes are observed in lupus nephritis (LN) in our previous study. This study aimed to explore mitochondrial fission proteins expression in podocytes using bioinformatics analysis and further to investigate the associations between mitochondrial fission proteins and laboratory features in LN.

Methods: To determine the differentially expressed genes (DEGs) between LN and normal controls, we downloaded and analyzed microarray datasets. Then download the mitochondrial genes list from the MitoMiner 4.0 database, then take the genes that are common with the DEGs. Functional enrichment analyses were then performed. Then mitochondrial fission was observed through electron microscope. We performed immunofluorescence staining to explore the expression of mitochondrial fission proteins in LN patients.

Results: Among these 658 DEGs, 5 DEGs related to mitochondrial dynamics were identified. Mitochondrial dynamics proteins were involved in mitophagy. Mitochondrial fission proteins Drp1 and Fis1 staining were significantly enhanced compared to that in the controls. 24h-UTP are positively correlated with mitochondrial fission proteins expression.

Conclusion: Mitochondrial fission was observed in LN patients' podocytes. Mitochondrial fission proteins Drp1 and Fis1 were overproduced in podocytes, and then they can lead to mitochondrial fission, which may aggravate podocyte damage and proteinuria. While the mechanism still needs to be explored.

Keywords: lupus nephritis, podocyte injury, mitochondria fission, Drp1, Fis1

Introduction

Lupus nephritis (LN) accounts for approximately 50% of systemic lupus erythematosus (SLE) patients.[1] The glomerular injury is associated with different pathogeneses, and podocyte damage is common in various ISN/RPS class LN.[2] In podocyte, mitochondrial morphological changes are observed in lupus nephritis (LN). Different sized mitochondria increased and mitochondrial cristae disappeared in podocyte.[3] Some studies have found increased mitochondrial mass contributed to aberrant activation and enhanced necrosis of T cells in SLE.[4,5] Blocking Rab4 with 3-PEHPC results in the restoration of Drp1 and reverses mitochondrial accumulation, as well as the production of antinuclear antibodies, proteinuria, and lupus nephritis.[6] Inhibiting mitochondrial fission that can protect glomerular podocytes was found in diabetic kidney disease.[7] Aldosterone induced mitochondrial dysfunction and podocyte injury mediated by p53/Drp1-dependent mitochondrial fission.[8] Also, one study found mitochondrial fission promoted renal fibroblast activation and fibrogenesis in chronic kidney disease.[9] Whereas the relationship between mitochondrial fission and podocyte injury in LN still needs further experiments to explore. Bioinformatics analysis was used to identify DEGs related to

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mitochondrial dynamics in this study. Then we observed the mitochondrial fission through electron microscope. To explore the expression of mitochondrial fission proteins Drp1 and Fis1, immunofluorescence staining and semi-quantitative analysis were performed. The relationship between glomerular expression of mitochondrial fission proteins and clinical data was explored.

Methods

Microarray Data

NCBI-GEO[10] is a public functional genomics data repository. GSE 112943, GSE 113342, GSE 32591 were selected and downloaded. Total of 14 LN and 6 normal kidney biopsy samples were contained in GSE113342 dataset.[11] And 32 LN and 14 normal biopsy samples in GSE 32591.[12] And 14 LN and 7 normal biopsy samples in GSE112943.[13]

Identification of DEGs

We used the GEO2R online tool to identify DEGs between LN and normal controls. We set log fold change (FC) >1 and P-value <0.05. Log FC <0 was considered downregulated, whereas log FC >0 was considered upregulated. Download the mitochondrial genes list from the MitoMiner 4.0 database.[14] The intersections of mitochondrial genes from 3 datasets are taken, and the resulting common DEGs are then combined.

Functional Enrichment

Gene Ontology (GO) function for analyzing genes biological processes and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were executed using the online biological information database database for Annotation, Visualization and Integrated Discovery (DAVID).[15–17] P <0.05 is considered statistically significant.

Patients

The study was approved by the Ethics Committee of the Fujian Provincial Hospital (K2021-04-046) and complies with the Declaration of Helsinki. This study included 30 lupus nephritis (LN) patients with a mean age of 32.70 ± 12.17 years. Six types of pathological classifications (Class II, III, IV, V, III+V, and IV+V) were used, with five patients in each group. Additionally, 15 patients with a mean age of 55.69 ± 7.27 years who underwent nephrectomization due to renal tumors were used as normal controls. Further details can be found in a previous study.[18]

Morphology of Mitochondria Was Observed

The kidney tissue of both LN patients and normal controls were preserved in ice-cold 1% glutaraldehyde in 0.1 M PBS for transmission electron microscopy. The samples were then sliced by laboratory staff, and the mitochondria and mitophagy were observed using a transmission electron microscopy.

Immunofluorescence Staining of Mitochondrial Fission Proteins

Renal biopsy specimens were embedded in an OCT mixture (Sakura, Hayward, CA, USA) and sliced into 5 μm frozen sections.[3] The mouse anti-Drp1 and Fis1 antibody (Proteintech Group, Inc., Chicago, IL, USA) were used. While rabbit anti-synaptopodin antibody (Proteintech Group, Inc. Chicago, IL, USA) was used as a podocyte marker for double immunofluorescence staining. Images were taken with a fluorescence microscope (Nikon Eclipse C1, Japan). The integral optical density (IOD) and the area ratio (AR) of the positively stained area to the glomerular area were used as semi-quantitative values to measure the expression of Drp1 and Fis1.[18,19]

Correlation of Drp1, Fis1 with Clinical and Laboratory Data

Thirty LN patients and fifteen healthy controls were used for this correlation analysis. The clinical data used in this study was obtained from the cohort used for fluorescence staining of mitochondrial fission proteins.

Statistical Analysis

The *t*-test or Mann–Whitney *U*-test were used to compare the differences between the two groups using SPSS. The $\chi 2$ test was used to calculate the ratio. A p-value of less than 0.05 was considered statistically significant.

Results

DEG Identification

A total of 12376 DEGs were identified from the GSE112943 dataset, including 9434 upregulated and 2942 downregulated genes. In the GSE113342 dataset, 68 DEGs were identified, including 42 upregulated and 26 downregulated genes. In the GSE32591 dataset, 171 DEGs were observed, consisting of 28 upregulated and 143 downregulated genes. After combining the three datasets, a total of 10045 DEGs were found, with 658 DEGs being common between the datasets and mitochondrial genes, as shown in the Venn diagram (Figure 1a). The 658 DEGs consisted of 142 downregulated genes and 516 upregulated genes. These DEGs associated with mitochondrial dynamics are plotted in Figure 1b, and the basic information of 5 DEGs related to mitochondrial dynamics are shown in Table 1.

GO Annotation and KEGG Pathway Enrichment Analyses

The findings regarding GO and KEGG are presented in Table 2 and Figure 2. GO biological process analysis revealed that the 658 DEGs were significantly linked to apoptotic process and translation. The top three significant changes in cell component were observed in mitochondrion, peroxisome and ribosome. The primary changes in molecular function were associated with RNA binding. KEGG pathway analysis indicated that the DEGs were mainly associated with metabolism and biosynthesis. We also found mitochondrial dynamics proteins are involved in mitophagy.

Mitochondrial Fission

Mitochondria in the podocytes from health control showed ellipsoid shape. And cristae could be seen clearly in mitochondria. While, different sized mitochondria were observed in podocytes of LN patients, mitochondrial cristae were disappeared. Through the electron microscope, we found that mitochondrial ridge structure is damaged (Figure 3).

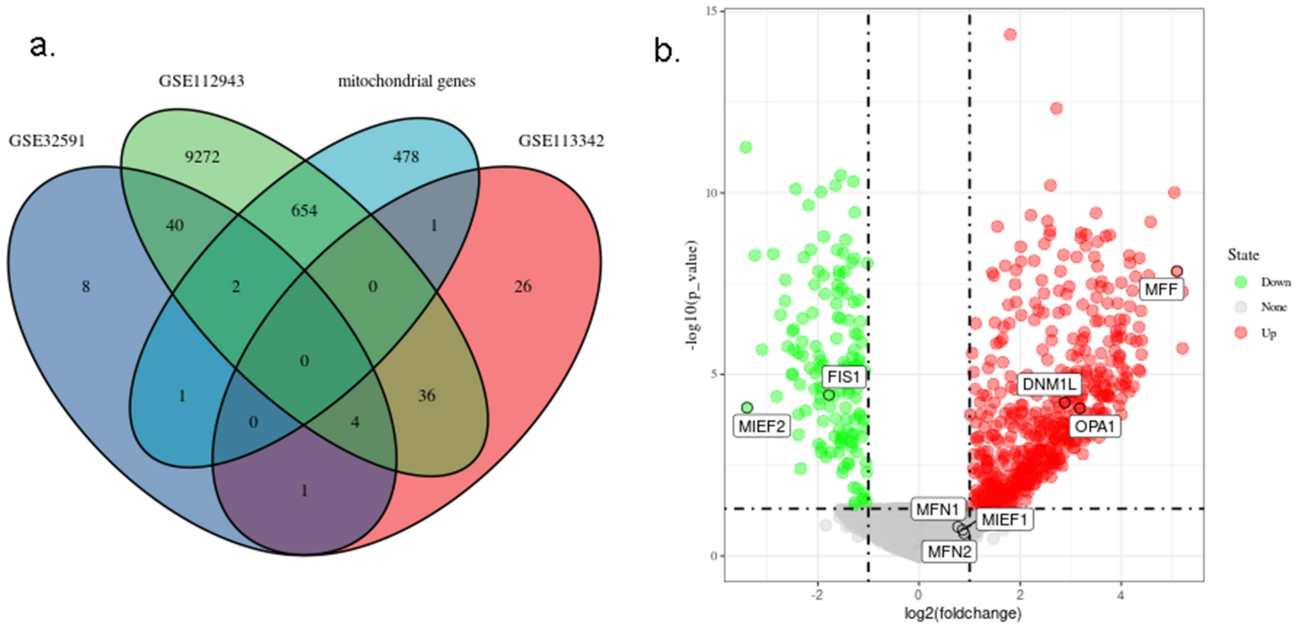

Figure 1 Identification of common DEGs from GSE32591, GSE112943, GSE113342 datasets and mitochondrial genes. (**a**) Venn diagram of DEGs based on the three GEO datasets and mitochondrial genes. (**b**) Volcano plot of DEGs. Red, upregulation; green, downregulation.

Table 1 Basic Information on the 5 DEGs Related to Mitochondrial Dynamics

ID	P.Value	logFC	Gene. symbol	Gene.title	Synonyms	Function	Regulation
ILMN_1724826	5.97E-05	2.88	DNM1L	dynamin 1 like	DLP1, DRP1, DVLP, DYMPLE, EMPF, EMPF1, HDYNIV, OPA5, O00429, gene:10059	Mitochondrial fission	UP
ILMN_1658351	3.69E-05	−1.78	FIS1	fission, mitochondrial 1	CGI-135, TTC11, Q9Y3D6, gene:51024		DOWN
ILMN_2198408	1.07E-02	1.48	MFF	mitochondrial fission factor	C2orf33, EMPF2, GL004, Q9GZY8, gene:56947		UP
ILMN_1793203	1.94E-01	0.86	MIEF1	mitochondrial elongation factor 1	AltMIEF1, HSU79252, MID51, MIEF1-MP, SMCR7L, dJ1104E15.3, Q9NQG6, gene:54471		UP
ILMN_1815923	8.27E-05	−3.4	MIEF2	mitochondrial elongation factor 2	MID49, SMCR7, Q96C03, gene:125170		DOWN
ILMN_1664186	3.24E-02	−0.27	MFN1	mitofusin 1	hfzo1, hfzo2, Q8IWA4, gene:55669	Mitochondrial fusion	DOWN
ILMN_1651385	4.73E-02	0.30	MFN2	mitofusin 2	CMT2A, CMT2A2, CMT2A2A, CMT2A2B, CPRP1, HMSN6A, HSG, MARF, O95140, gene:9927		UP
ILMN_1729775	8.59E-05	3.18	OPA1	OPA1, mitochondrial dynamin like GTPase	BERHS, MGM1, MTDPS14, NPG, NTG, largeG, O60313, gene:4976		DOWN

Table 2 KEGG Pathway Enrichment Analysis of DEGs in LN Glomerulus (Partial)

Term	Description	Count in Gene Set	P-value
hsa05208	Chemical carcinogenesis - reactive oxygen species	38	1.71E-13
hsa03010	Ribosome	23	4.25E-07
hsa04146	Peroxisome	22	7.50E-12
hsa04723	Retrograde endocannabinoid signaling	17	3.55E-04
hsa04210	Apoptosis	16	4.35E-04
hsa04215	Apoptosis - multiple species	12	2.80E-08
hsa04260	Cardiac muscle contraction	12	8.05E-04
hsa01524	Platinum drug resistance	11	7.33E-04
hsa04115	p53 signaling pathway	10	0.00282698
hsa03320	PPAR signaling pathway	10	0.00340466
hsa04137	Mitophagy - animal	8	0.02758685
hsa00670	One carbon pool by folate	6	0.00104999
hsa03410	Base excision repair	5	0.04460447
hsa04122	Sulfur relay system	3	0.03987771

Abbreviations: KEGG, Kyoto Encyclopedia of Genes and Genomes; DEGs, differentially expressed genes.

Expression of Drp1 and Fis1 in Various ISN/RPS Class LN Patients

Immunofluorescence microscopy revealed that the glomerular staining of Drp1 in health controls was negative, while the staining in patients with class IV+V was weak. In Class III+V, the Drp1 proteins were found to colocalize with the podocyte marker synaptopodin (Figure 4). The staining of Fis1 in health control was very weak, but it was significantly enhanced in Class III and Fis1 was also found to colocalize with the synaptopodin marker (Figure 5). The semi-quantitative analysis of the results is presented in Table 3 and Figure 6.

Correlation of Drp1 and Fis1 with Laboratory Data

The IOD of Drp1 was found to be positively correlated with C3, C4 and 24h-UTP. The AR of Fis1 was positively correlated with BUN and 24h-UTP, while the IOD of Fis1 was negatively correlated with 24h-UTP. However, no correlation was observed between the AR of Drp1 and laboratory data. We analyzed the association between Drp1 and Fis1 and clinical measures in patients with different pathological types of lupus nephritis. And we can see that there is no significant correlation between the clinical indicators of patients with type IV lupus nephritis and DRP1 and Fis1. The results are presented in Figures 7 and 8.

Discussion

Bioinformatics analysis was used to identify 5 DEGs related to mitochondrial dynamics, including 4 mitochondrial fission genes (DNM1L, FIS1, MFF and MIEF2) and 1 mitochondrial fusion gene (OPA1).

Enrichment analysis revealed that mitochondrial dynamics proteins were involved in mitophagy. Electron microscopy showed that mitochondrial fission and mitochondrial autophagy were present, suggesting that mitochondrial dynamics and mitophagy may be involved in the pathogenesis of proteinuria in LN. Literature suggests that the regulation of mitochondrial dynamics is linked to the initiation of mitophagy.[20] It is widely accepted that mitochondrial fission plays a crucial role in facilitating mitophagy in various types of mammalian cells. The primary regulator responsible for

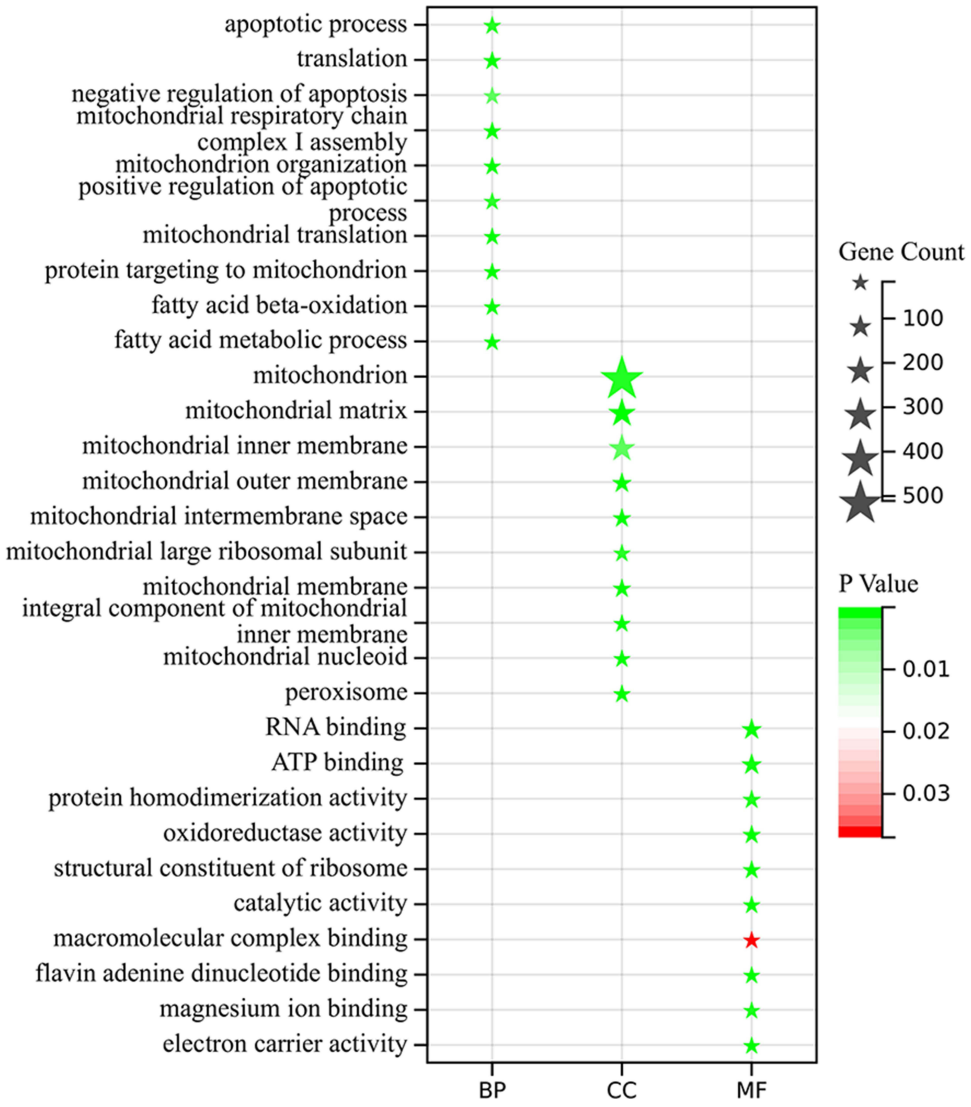

Figure 2 GO annotation analyses. The DEGs enrichment of BP, MF, CC (The top ten, $P < 0.05$).

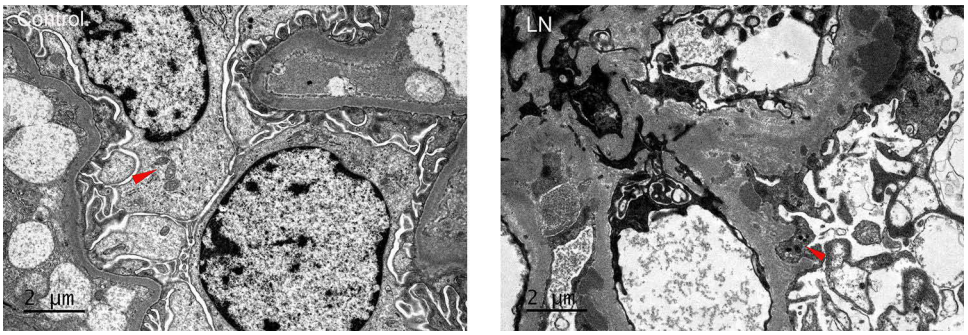

Figure 3 Mitochondrial fission. Red arrows represented the fission mitochondria.

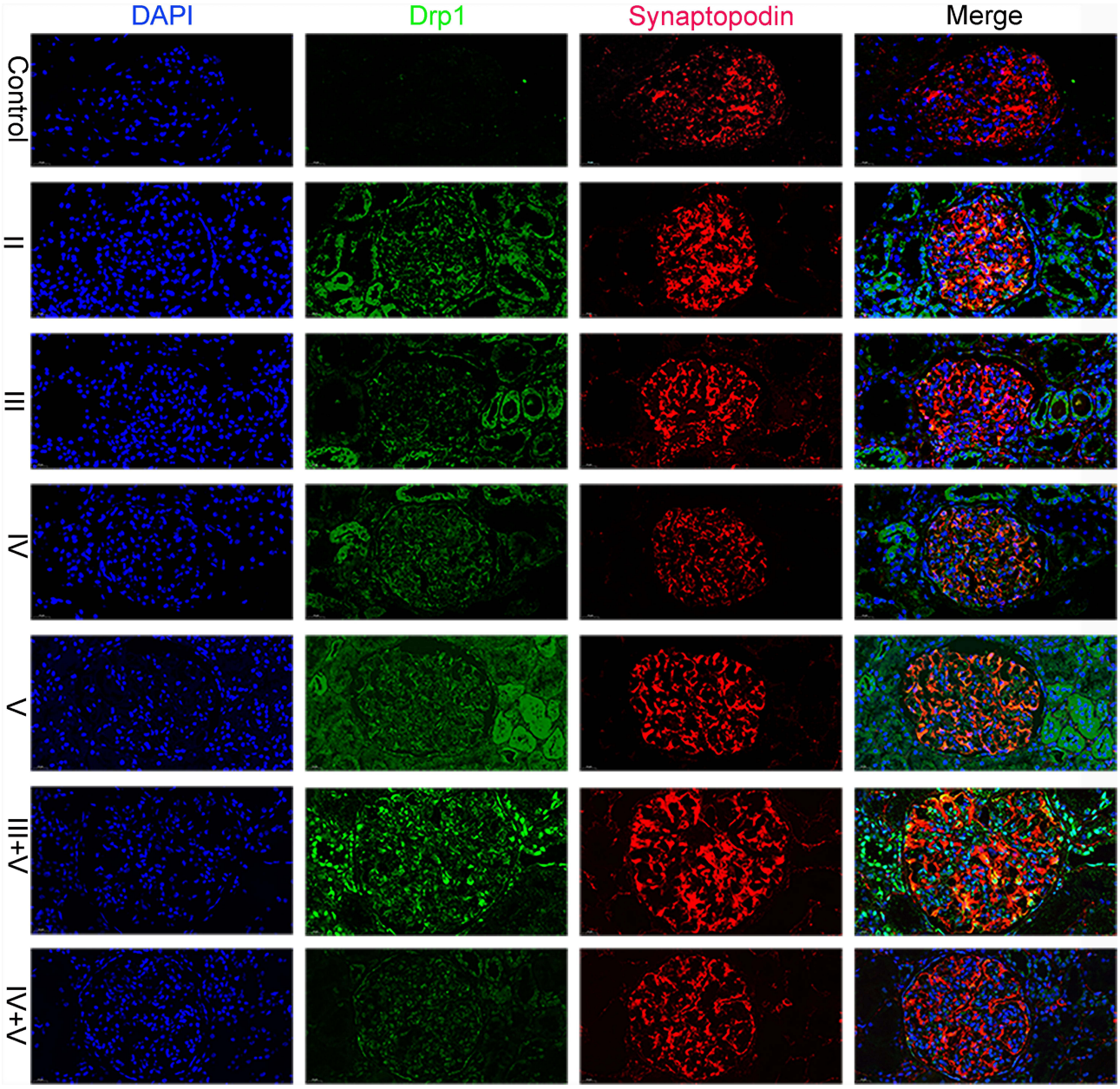

Figure 4 Expression of Drp1 in various ISN/RPS class LN patients. Glomerular staining of Drp1 was markedly enhanced in LN patients. The Drp1 proteins colocalized with the podocyte marker synaptopodin especially in class III+V.

mitochondrial fission is Drp1. It is a cytosolic protein, undergoes translocation to the mitochondrial outer membrane to initiate the fission process. In the absence of Drp1-mediated mitochondrial division, mitochondria exhibit increased connectivity and size, leading to impaired mitophagy in the heart and brain of mice.[21] Meanwhile, one study found that Drp1 translocated to mitochondria and was phosphorylated at S616 in response to ischemia/reperfusion injury (IRI). Inhibiting Drp1 phosphorylation significantly suppressed without affecting general autophagy suggesting that Drp1 was involved the process of mitochondrial fragmentation and downregulation of mitophagy significantly aggravated kidney dysfunction indicating that mitophagy was activated via Drp1-dependent pathway to protect cells from IRI-induced apoptosis.[22] And the role of mitochondrial fission on mitophagy remains to be determined.

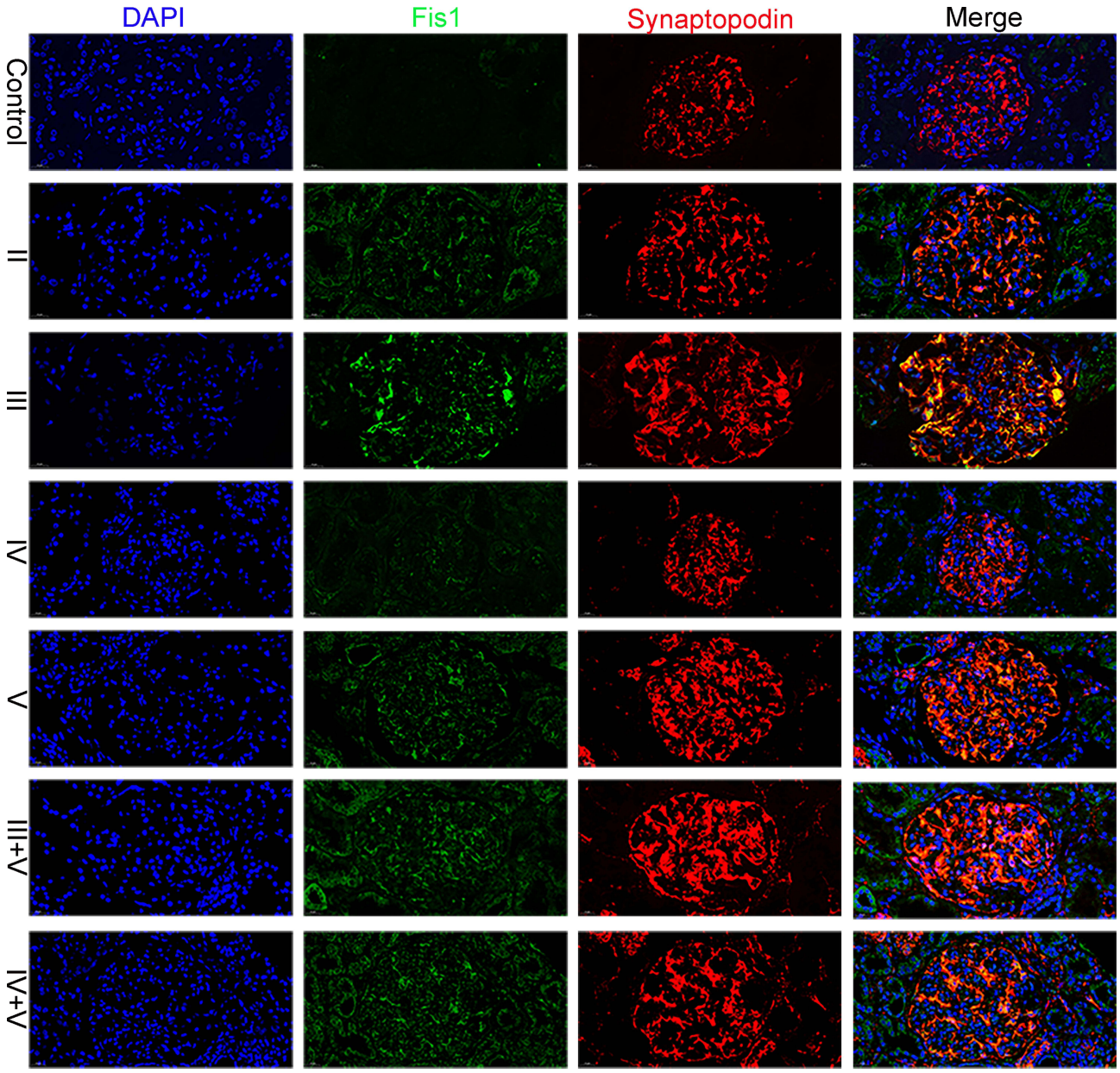

Figure 5 Expression of Fis1 in various ISN/RPS class LN patients. Glomerular staining of Fis1 was markedly enhanced in LN patients. The Fis1 proteins colocalized with the podocyte marker synaptopodin especially in class II.

We then proceeded to further investigate the expression of Drp1 and Fis1 in the glomerulus. Our findings showed that the staining of Drp1 and Fis1 in Lupus patients was significantly increased and they colocalized with the podocyte marker synaptopodin. Moreover, 24h-UTP was positively correlated with Drp1 and Fis1. Mitochondria are dynamic organelles that change their morphology through fission and fusion in order to maintain their function. The majority of viewpoints suggest that excessive mitochondrial fission leading to mitochondrial fragmentation is an inevitable stage of cell apoptosis. Mitochondrial fragmentation results in an increased permeability of the mitochondrial outer membrane, leading to the release of cytochrome c from the mitochondria. Cytochrome c is a crucial apoptotic trigger that can activate caspase enzymes, thus promoting apoptosis.[23]

Our previous study found that in the doxorubicin rat kidney disease model, the expression of Drp1 and Fis1 increased in glomerular podocytes. We overexpressed Drp1 in podocytes and found that mitochondrial fission increased and

Table 3 Glomerular Expression of Drp1 and Fis1 in Various ISN/RPS Class LN Patients

Group	Drp1		Z P value (Control vs LN)		Fis1		Z P value (Control vs LN)	
	AR	DOI	AR	DOI	AR	DOI	AR	DOI
Control	0.002 (0.001,0.018)	0.044 (0.027,0.354)	NA NA	NA NA	0.022 (0.009,0.049)	0.603 (0.080,1.115)	NA NA	NA NA
LN patients	0.094 (0.052,0.152)	28.977 (23.174,37.002)	−5.148 <0.001	−5.876 <0.001	0.0816 (0.038,0.156)	23.853 (17.065,31.821)	−3.628 <0.001	−6.421 <0.001
Class II	0.124 (0.076,0.169)	32.598 (28.653,41.547)	−4.445 <0.001	−4.491 <0.001	0.082 (0.023,0.122)	20.413 (14.464,24.591)	−2.511 0.011	−4.815 <0.001
Class III	0.039 (0.019,0.067)	20.701 (13.800,38.381)	−2.977 0.003	−4.031 <0.001	0.088 (0.033,0.157)	14.907 (10.234,30.269)	−2.140 0.033	−4.398 <0.001
Class IV	0.082 (0.047,0.128)	31.108 (29.448,33.220)	−2.717 0.007	−2.944 0.003	0.048 (0.021,0.161)	18.435 (11.843,25.035)	−1.214 0.249	−3.330 <0.001
Class V	0.070 (0.015,0.146)	25.181 (17.679,35.157)	−3.722 <0.001	−4.963 <0.001	0.054 (0.037,0.162)	26.378 (20.931,35.938)	−2.662 <0.001	−4.815 <0.001
Class III+V	0.151 (0.064,0.293)	36.139 (25.511,42.381)	−4.723 <0.001	−5.000 <0.001	0.091 (0.044,0.263)	27.811 (17.718,38.494)	−3.078 0.002	−4.815 <0.001
Class IV+V	0.090 (0.058,0.121)	26.436 (23.996,30.059)	−4.654 <0.001	−5.157 <0.001	0.108 (0.039,0.256)	32.062 (21.428,37.895)	−3.229 0.001	−4.815 <0.001

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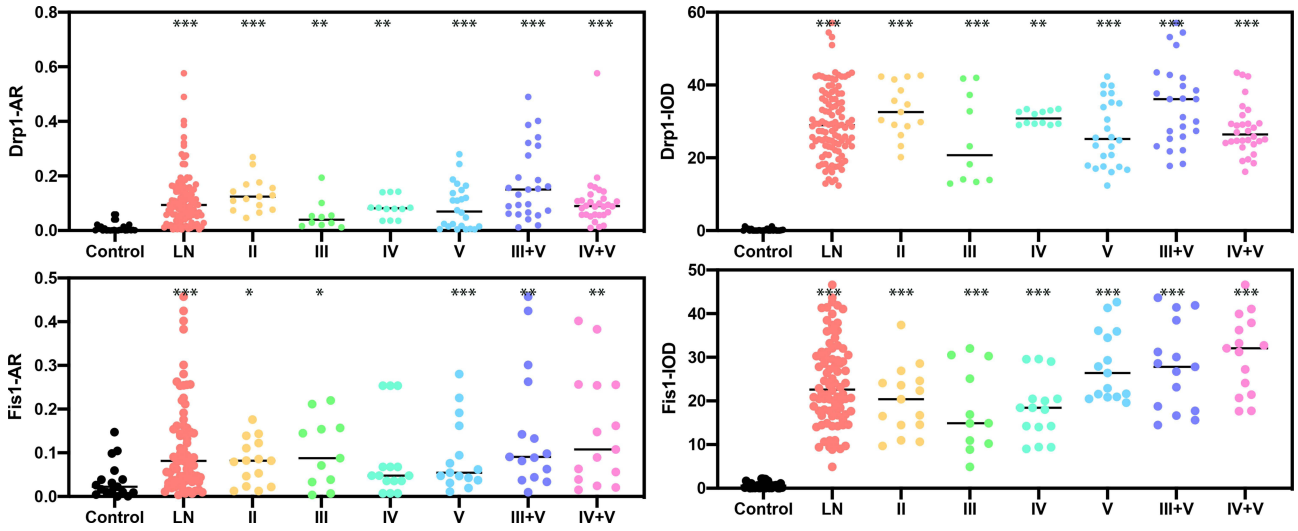

Figure 6 Glomerular expression of Drp1 and Fis1 in various ISN/RPS class LN patients.
Note: *P < 0.05, **P < 0.01, *** P < 0.001.

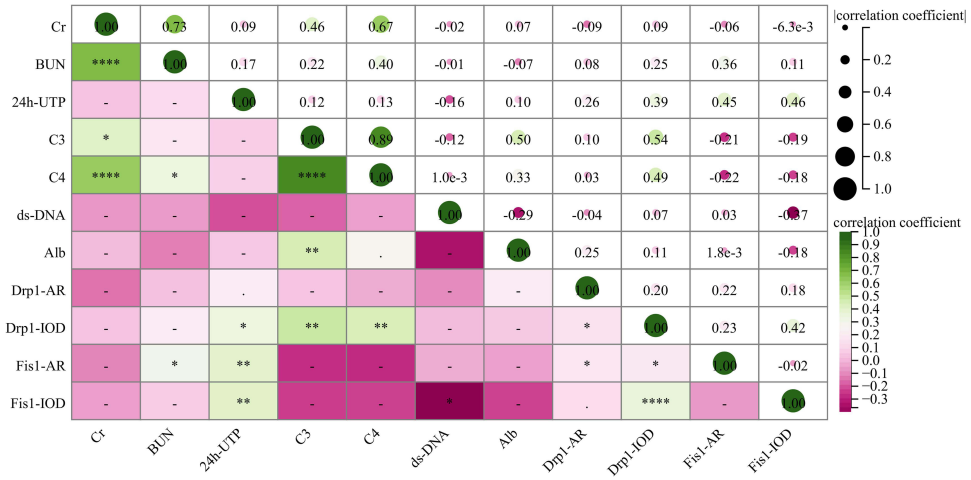

Figure 7 The correlation of mitochondrial fission proteins and laboratory data.
Note: *P < 0.05, **P < 0.01, *** P < 0.001, ****P < 0.0001.

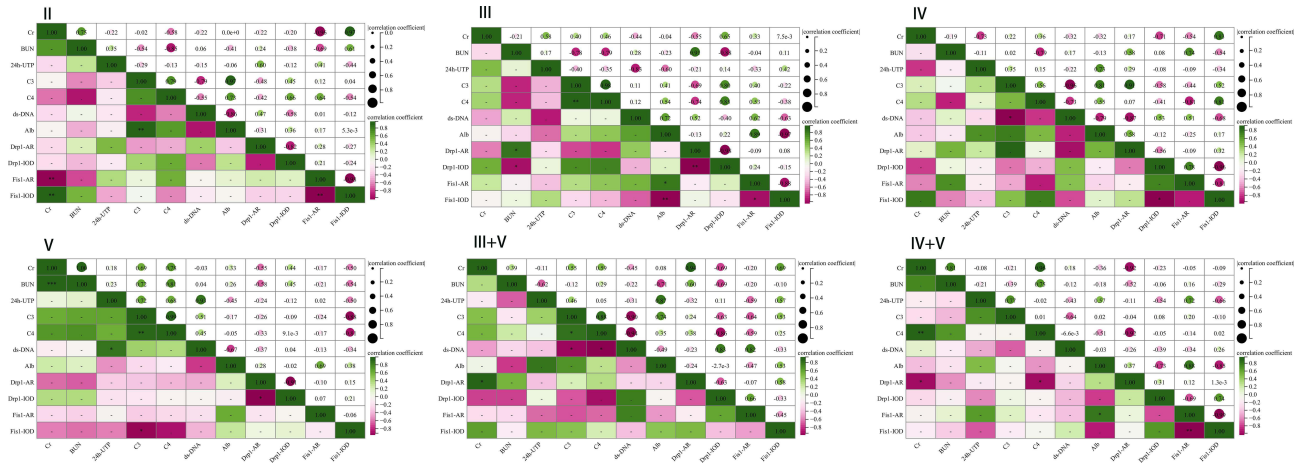

Figure 8 The correlation of mitochondrial fission proteins and laboratory data in different pathological types.
Note: No significant correlation between the clinical indicators of patients with type IV lupus nephritis and DRP1 and Fis1. *P < 0.05, **P < 0.01, *** P < 0.001, ****P < 0.0001.

podocyte apoptosis increased.[19] Downregulation of Drp1 and Fis1 can inhibit mitochondrial fission and prevent high glucose-induced apoptosis in retinal endothelial cells.[24] Our findings suggest that increased expression of Drp1 and Fis1 leads to mitochondrial fission, which aggravates podocyte damage and the occurrence of proteinuria. However, the specific mechanism still needs to be explored.

Conclusions

Among the 658 DEGs identified, 5 DEGs related to mitochondrial dynamics were identified. Enrichment analysis revealed that mitochondrial dynamics proteins were involved in mitophagy. 24h-UTP was found to be positively correlated with the expression of mitochondrial fission proteins. We hypothesize that increased expression of mitochondrial fission proteins leads to mitochondrial fission, which aggravates podocyte damage and proteinuria. However, the underlying mechanism still needs to be further explored.

Ethics Approval and Consent to Participate

The studies involving human participants were reviewed and approved by the ethics committee of Fujian Provincial Hospital, and all participants provided their written informed consent prior to their involvement.

Consent for Publication

Written informed consent for publication was obtained from all participants.

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Disclosure

The authors declare that there are no commercial or financial relationships that could be construed as a potential conflict of interest.

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