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Original Paper

Overproduction of Mitochondrial Fission Proteins in Membranous Nephropathy in Children

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Key Words
Nephrotic syndrome • Podocyte • Mitochondrial fission proteins

Abstract
Background/Aims: The molecules involved in nephrotic syndrome (NS) have not been fully clarified. Mitochondrial fission proteins are found to be involved in podocyte injury *in vitro*. Increased glomerular expression of mitochondrial fission proteins was found in adriamycin nephropathy in our previous study. Whether or not mitochondrial fission proteins are involved in podocyte injury in NS is not clear. This study explored the glomerular expression and possible pathological significance of mitochondrial fission-associated proteins, including dynamin-related protein 1 (Drp1) and mitochondrial fission protein 1 (Fis1), in children with NS. ***Methods:*** Eighteen children with primary NS, including 6 with minimal change disease, 6 with focal segmental glomerulosclerosis, 6 with membranous nephropathy, 6 children with isolated haematuria and 3 normal controls were included. The glomerular expression of Drp1, phospho-Drp1 (Ser616) and Fis1, urinary protein measurements, and podocyte mitochondrial density under electron microscopy were investigated and compared. ***Results:*** Glomerular expression of Drp1, phospho-Drp1 (Ser616) and Fis1 was mainly increased in children with NS with membranous nephropathy. No relationship was found between glomerular expression of Drp1, phospho-Drp1 (Ser616) and Fis1 and podocyte mitochondrial density or urinary protein measurements. ***Conclusion:*** Glomerular overproduction of Drp1, phospho-Drp1 (Ser 616) and Fis1 occurred mainly in children with membranous nephropathy. The pathological significance deserves further investigation.

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Introduction

Nephrotic syndrome (NS) is a common renal disease in children, especially in Asian countries. Heavy proteinuria is the most prominent feature of NS. There is a limited availability of drugs for the control of proteinuria in the clinic. Dysfunction of the glomerular filtration barrier, especially by podocyte injury, has been confirmed to be key in the development of proteinuria. However, the mechanism of podocyte injury is not fully understood. Many molecules and organelles with different roles have been found to be involved in podocyte injury and in development of proteinuria, such as slit diaphragm molecules, cytoskeleton molecules, integrins and mitochondria [1-4].

The disturbance of mitochondrial dynamics, especially mitochondrial fragmentation, has been found to be closely associated with apoptosis in various types of cells. The fragmentation of mitochondria can lead to the release of apoptotic trigger factors, such as cytochrome c, from the mitochondria to induce apoptosis [5-8]. Mitochondrial fission is mainly regulated by mitochondrial fission associated proteins including dynamin-related protein 1 (Drp1) and mitochondrial fission protein 1 (Fis1) [9-11], among which Drp1 is a key protein. The promitochondrial fission role of Drp1 is regulated by many modifications, including sumoylation, ubiquitination, S-nitrosylation, and especially phosphorylation [12]. Drp1 has two major phosphorylation sites, Ser637 and Ser616. The phosphorylation of Drp1 on Ser616 facilitates the fission of mitochondria, while the phosphorylation of Drp1 on Ser637 plays the opposite role [13, 14].

In previous studies, we [15] and other groups [16, 17] observed that mitochondrial fragmentation was involved in podocyte injury in cultured podocytes. In addition, our previous study found a correlation between the overproduction of glomerular mitochondrial fission proteins, including Drp1, phospho-Drp1 (Ser616) and Fis1, and proteinuria in adriamycin nephropathy in rats [18]. It seems that mitochondrial fission proteins are novel players in proteinuria. However, it is not clear whether or not glomerular expression of mitochondrial fission proteins change in children with NS. The pathological significance of mitochondrial fission proteins in children with NS also deserved further exploration.

In this study, the glomerular expression of Drp1, phospho-Drp1 (Ser616) and Fis1 in children with NS of different pathological types and their possible relationship with proteinuria and podocyte mitochondrial density were investigated.

Materials and Methods

Patients

All protocols were approved by the Ethics Committee of Peking University First Hospital. Eighteen children with primary NS, with a mean age of 11.1 ± 4.3 years, were included, including 6 children with minimal change disease (MCD), 6 children with membranous nephropathy (MN), and 6 children with focal segmental glomerulosclerosis (FSGS). All children with NS had no evidence of genetic diseases (Table 1). All children with NS had normal serum complement C3 and C4 levels. Six children with haematuria, with an age of 7.8 ± 4.5 years, were also included as disease controls. All children with NS underwent renal biopsy for pathological diagnosis due to poor response to treatment or suspicion of non-MCD pathological change. Cryosections of renal biopsy specimens were made. Normal renal tissues from 3 patients with a mean age of 33.3 ± 26.5 years who underwent nephrectomization due to renal tumours were used as normal controls. The clinical data of the children with NS are shown in Table 1. The quantified 24-hour urinary protein results (mg/kg) were collected during 1 week of renal biopsy.

Table 1. Clinical data of the patients with nephrotic syndrome and semi-quantitative mitochondrial fission protein results. Drp1, dynamin-related protein 1; Fis1, mitochondrial fission protein 1; P-Drp1, phospho-Drp1(Ser 616); DD, disease duration (month); UP, 24 h urinary protein (mg/kg); IS, immunosuppressant; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MN, membranous nephropathy; SR, steroid resistant; SS, steroid sensitive; FR, frequent relapse; LSR, late steroid resistant; /, not available; a, urinary protein 4+; b, next-generation sequencing; Lef, Leflunomide; CsA, cyclosporine; CTX, cyclophosphamide; MMF, mycophenolate mofetil; Tac, tacrolimus

Pathology	Patients	Age (yr.)	Drp1	Fis1	P-Drp1	DD	UP	Genetic analysis	Steroid response	IS
FSGS	LMX	9	0	0	0	32	63	NPHS2 (-)	SR	Lef，CsA
	LYJ	1	0	0	0	1	/ [a]	NPHS1 (-)	SR	None
	LLZ	9	0	0.3	0.5	24	85	(-) [b]	SR	CTX, MMF, CsA
	YYX	11	0	0	0	3	121	/	SR	CTX, MMF
	ZXX	6	0	0	0	18	214	/	SR	Tac, MMF, CTX
	ZQR	6	0	0	0	33	232	/	SR	Tac, CTX, MMF
	ZZR	14	0.5	0.1	0.2	108	111	/	SS, FR	CTX, CsA, Tac
MCD	LYL	11	0	0.6	0	4	112	/	SS, FR, LSR	Tac
	NZT	6	0.3	1.0	0.9	50	91	/	SS, FR	CsA, MMF
	WHY	13	0	0.1	0	1	85	/	SR	None
	LXC	9	0	0.1	0	15	264	/	SS, FR	CSA
	LWQ	13	0	0	0	3	138	/	SR	None
MN	ZYZ	15	3.7	1.1	1.4	43	70	/	SR	CTX, CsA
	JGW	18	3.5	1.0	0.8	16	49	/	SR	Tac
	CRZ	14	4.0	1.1	0.7	1	109	/	/	None
	CTC	15	1.9	3.2	1.3	76	147	/	SR	None
	HJB	12	2.9	3.7	3.8	1.5	161	/	SR	None
	HZQ	17	3.8	2.9	2.0	1	120	/	/	None

Immunofluorescence staining of glomerular Drp1, phospho-Drp1 (Ser616) and Fis1

Renal biopsy specimens were embedded in an OCT mixture (Sakura, Hayward, CA, USA) and sliced into 5 μm frozen sections. Immunofluorescence staining was performed according to previously reported protocols [15]. Rabbit anti-Drp1 (Cell Signal Technology Inc. Beverly, MA, USA), rabbit anti-phospho-Drp1 (Ser616) (Cell Signal Technology Inc. Beverly, MA, USA) and rabbit anti-Fis1 (Thermo Fisher Scientific, Waltham, MA, USA) antibodies were used. A mouse anti-synaptopodin antibody (Novus Biologicals, Littleton, CO, USA) was used as a podocyte marker for double immunofluorescence staining. A goat anti-rabbit IgG/Alexa Fluor 488 antibody and a goat anti-mouse IgG/Alexa Fluor 594 antibody (ZSGB-BIO, Beijing, China) were used to visualize different proteins. Images were collected using confocal immunofluorescence microscopy (Olympus Fluoview FV 1000, Tokyo, Japan). Blinded semi-quantitative analysis was performed three times by one person. The average score of three replicates was used as the quantification result for the target molecule. During semi-quantitative analysis, the glomerulus was divided into four quadrants and scored according to the positive staining area: negative or very weak staining was scored as 0, 25% positive staining was scored as 1, 26% to 50% positive staining was scored as 2, 51% to 75% positive staining was scored as 3, and > 75% positive staining was scored as 4. The average score of all glomeruli was used as the quantitative result for each molecule.

Podocyte mitochondrial density analysis of patients under electron microscopy

Podocyte mitochondrial density was analysed according to our previous report [15]. Ultrathin sections of patient samples, including 9 patients (3 MCD, 3 FSGS, and 3 MN) with NS and 3 patients with haematuria, were photographed with a transmission electron microscope (JEOL-1230, Tokyo, Japan). Thirty photographs were collected from each patient according to the rule of equidistant zigzag movement under a magnification of 25 000 in the glomerular area. An average of 66 mitochondria from each patient were analysed with Scandium Image Processing software (Olympus Soft Imaging Solutions, Munster, Germany). Mitochondrial density in podocyte cytoplasm was measured.

Statistical analysis

SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA) was used. Data were expressed as the mean ± standard deviation (mean ± SD) or median (min, max). One-way ANOVA with the LSD post hoc test or the Kruskal-Wallis test with the Bonferroni test was used to compare differences among the multiple groups, depending on the distribution of the data. Student's t-test or the Mann-Whitney U test was used to compare differences between two groups. Spearman correlation analysis was performed between mitochondrial density and glomerular fission protein expression level. A P value of < 0.05 was considered statistically significance.

Results

Clinical and laboratory information for the patients

No significant difference in age at renal biopsy was found among the NS group, the haematuria group and the normal controls. In children with NS, no significant difference in 24 h urinary protein measurements (mg/kg) was found among the groups with MCD (133.5 ± 66.6 mg/kg), MN (109.3 ± 43.3 mg/kg) and FSGS (143.0 ± 76.2 mg/kg). No significant difference in disease duration was found among the groups of NS children with MCD, MN, and FSGS (Tables 1 and 2). All children with NS had normal blood pressure.

Induction of glomerular Drp1, phospho-Drp1 (Ser616) and Fis1 in children with NS

By immunofluorescence microscopy, the glomerular staining of Drp1 and phospho-Drp1 (Ser616) in the controls was negative, and the glomerular staining of Fis1 was very weak. The glomerular staining of Drp1, phospho-Drp1 (Ser 616) and Fis1 was similar to that of the controls in patients with haematuria, MCD and FSGS. In 6 of 6 children with MN, the glomerular staining of Drp1, phospho-Drp1 (Ser 616) and Fis1 was obviously enhanced. Overproduced glomerular Drp1, phospho-Drp1 (Ser616) and Fis1 proteins were distributed along the glomerular capillary wall and co-localized with the podocyte marker synaptopodin (Fig. 1).

In the semi-quantitative analysis, no significant differences were found in the glomerular expression of the mitochondrial fission proteins between the group with NS, the group with haematuria and the normal control. In children with NS, a significant increase in Drp1, phospho-Drp1(Ser 616) and Fis1 was observed in the group of children with MN compared with the groups with MCD or FSGS (Table 2). No significant correlation between glomerular expression of the mitochondrial fission proteins and 24 h urinary protein level was found.

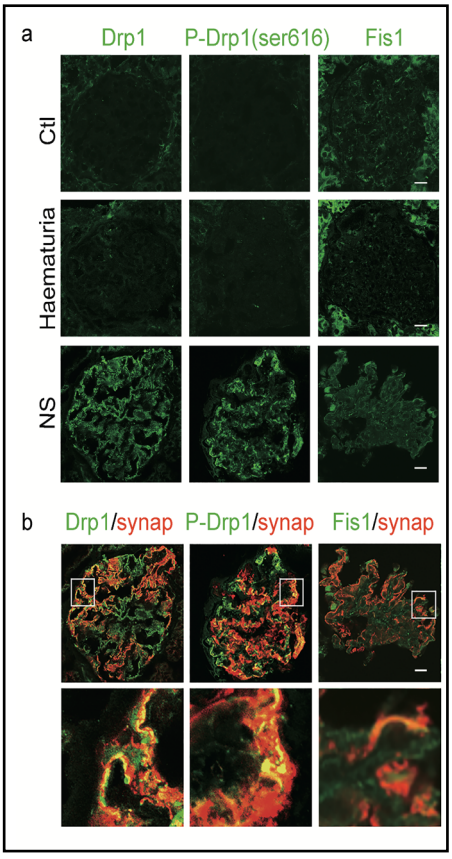

Fig. 1. Glomerular expression of Drp1, phospho-Drp1 (Ser616) and Fis1 in children with membranous nephropathy (MN). Drp1, Dynamin-related protein 1; P-Drp1 (Ser616), Phosphorylated Drp1 at serine 616; Fis1, mitochondrial fission protein 1; synap, synaptopodin. Ctl, normal control; NS, nephrotic syndrome. Sections stained for Drp1, P-Drp1(Ser616) and Fis1 were double stained for the podocyte marker synaptopodin (red colour). Glomerular staining of Drp1, P-Drp1(Ser616), and Fis1 increased in NS children with MN and co-localized with the podocyte marker synaptopodin. (Confocal immunofluorescence microscopy, Original objective 60×, bar=100 μm).

Table 2. Comparison of urinary protein, mitochondrial density and mitochondrial fission protein data in children with NS with different pathological changes. FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MN, membranous nephropathy; UP, urinary protein; Drp1, dynamin-related protein 1; Fis1, mitochondrial fission protein 1; *, Compared with MCD or FSGS, P < 0.0167

Group	24 h UP (mg/kg) Mean ± SD	Disease duration (month) Median (min, max)	Mitochondrial density Mean ± SD	Drp1 Median (min, max)	P-Drp1 (Ser 616) Median (min, max)	Fis1 Median (min, max)
FSGS	143.0 ± 76.2	21.0 (1, 33)	0.11 ± 0.01	0.0	0.0 (0.0, 0.5)	0.0 (0.0, 0.3)
MCD	133.5 ± 66.6	9.5 (1,108)	0.08 ± 0.02	0.0 (0.0, 0.5)	0.0 (0.0, 0.9)	0.1 (0.0, 1.0)
MN	109.3 ± 43.3	8.8 (0.5, 76)	0.08± 0.02	3.6 (1.9, 4) *	1.4 (0.7, 3.8) *	2.0 (1.0, 3.7) *

Comparison of podocyte mitochondrial density among patients with different pathologies

No significant differences in the podocyte mitochondrial density in podocyte cytoplasm were found among NS children with MCD, MN and FSGS (P = 0.144, Table 2, Fig. 2). There was no correlation of the glomerular expression of Drp1 (r = -0.546, P = 0.128), phospho-Drp1(Ser 616) (r = -0.259, P = 0.501) and Fis1 (r = -0.313, P = 0.412) with podocyte mitochondrial density in children with NS.

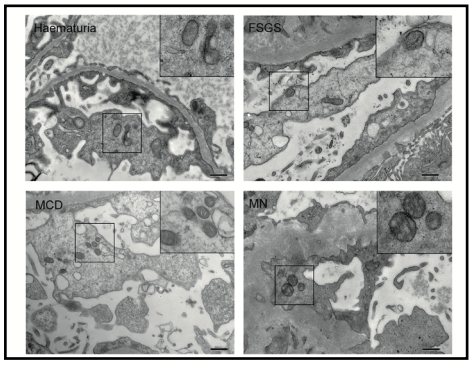

Fig. 2. Podocyte mitochondrial morphology in children from different groups. FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MN, membranous nephropathy. No significant differences in mitochondrial density were found between children with FSGS, MCD and MN. (Electron microscopy, bar=0.5 μm).

Discussion

Podocyte protection is a key strategy for the control of proteinuria in NS. However, the mechanism of podocyte injury is not fully understood. Some drugs are available for the control of proteinuria in the clinic, including corticosteroid, cyclosporine, tacrolimus, cyclophosphamide, mycophenolate mofetil, angiotensin conversion enzyme inhibitors, statins, Vitamin D, and Rituximab. However, some children with NS do not respond to current therapies and are at higher risk of developing end stage renal disease. Further investigation into the mechanism of podocyte injury is truly needed. Based on our previous observation that mitochondrial fragmentation participated in podocyte injury [15] and that overproduced Drp1 and Fis1, which can facilitate mitochondrial fragmentation, was observed in adriamycin nephropathy in rats [18], we further investigated whether or not glomerular mitochondrial fission proteins change in children with NS in this study.

In this study, several new findings were reported. First, we clearly found a significant increase in glomerular Drp1, phospho-Drp1 (Ser 616) and Fis1, mainly in children with MN, but not in children with MCD and FSGS, children with haematuria or normal controls. The co-localization of these molecules with the podocyte marker synaptopodin implied a podocyte origin of these molecules. Further investigations of different aspects of clinical manifestation were performed to determine the underlying cause of this phenomenon. From the clinical perspective, no significant difference in the age of onset was found among children with NS, children with haematuria, and normal controls. In children with NS, no significant differences in disease duration before renal biopsy or 24 h urinary protein measurements at the time of renal biopsy were found among children with MCD, FSGS and MN. The quantitative urinary protein results did not correlate significantly with the glomerular expression of mitochondrial fission-associated proteins in NS children. With respect to the possible effect of treatments on mitochondrial fission-associated proteins, no definite conclusion can be drawn at this time. The effect of cyclosporine A on the expression of Drp1 was reported in renal tubular

cells by de Arriba et al. [19], who reported that cyclosporine A induced expression of Drp1 in renal tubular cell. In our study, among children with MN, 1 child received treatment with cyclosporine A, 1 child received treatment with tacrolimus, and the other 4 children did not receive treatment with cyclosporine A or tacrolimus. However, all children with MN exhibited increased glomerular staining of mitochondrial fission proteins, regardless of therapy, and so evidence for a therapeutic effect is lacking.

According to a report by Nigro et al. [20], hypertension could modify the expression of a mitochondrial molecule, uncoupling protein 2. Therefore, we investigated whether or not hypertension could influence the expression of mitochondrial fission proteins. However, all the children with NS in this study had normal blood pressure. In addition, we attempted to explore whether a glomerular increase in mitochondrial fission-associated proteins is associated with podocyte mitochondrial density. Unfortunately, no significant difference of mitochondrial density was found among children with MCD, MN or FSGS. No correlation between glomerular expression of mitochondrial fission-associated proteins and mitochondrial density was found. Taken together, glomerular mitochondrial fission-associated proteins seem to increase specifically in children with MN. No similar findings have been reported. Although the induction factors and the effects of increased glomerular expression of mitochondrial fission proteins remain to be determined, these findings provide a new target for further investigation of the mechanism of MN.

The role of Drp1 in MN warrants further investigation. Whether the increase in Drp1 observed in children with MN is the cause or result of MN is not clear. From the mechanism of MN, several autoantibodies, such as M-type phospholipase A2 receptor (PLA2R) antibodies and thrombospondin type 1 domain-containing 7A antibodies, have been found in the sera of patient, and prominent increases in PLA2R and IgG4 have been observed in glomeruli of patients [21]. Increases in glomerular mitochondrial fission-associated proteins might induce a dysregulated immune response. The relationship between Drp1 and the immune response in other cells has been explored. Wang et al. [22] reported that knocking out Drp1 leads to the induction of a subset of genes involved in the immune response. Baixauli et al. [23] reported that Drp1 could modulate T-cell receptor signalling. On the other hand, evidence from Shahni et al. [24] showed that abnormalities of signal transducer and activator of transcription 2, which is a component of the Janus kinase (JAK)-signal transduction and activation of transcription (STAT) cytokine signalling pathway, lead to abnormal phosphorylation of Drp1. The relationship between Drp1 and MN warrants further study.

Conclusion

This study investigated possible new players in podocyte injury and proteinuria in children from the perspective of mitochondrial fission-associated proteins and reports one main finding. We found that the glomerular expression of Drp1, phospho-Drp1(Ser 616) and Fis1 was increased significantly in children with MN. This finding provides new targets for further exploration of the mechanism of podocyte injury and proteinuria and deserves further attention. Drp1 inhibitors have become promising agents for treating neurodegenerative diseases, such as Alzheimer's disease and Huntington's disease [25]. The effects of Drp1 inhibitors on podocyte protection warrant further investigation.

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Disclosure Statement

No conflicts of interest exist related to the submission of this manuscript.

References

1 Noone DG, Iijima K, Parekh R: Idiopathic nephrotic syndrome in children. Lancet 2018;392:61-74.
2 Hodson EM, Wong SC, Willis NS, Craig JC: Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane Database Syst Rev 2016;10:CD003594.
3 Wakamatsu A, Fukusumi Y, Hasegawa E, Tomita M, Watanabe T, Narita I, Kawachi H: Role of calcineurin (CN) in kidney glomerular podocyte: CN inhibitor ameliorated proteinuria by inhibiting the redistribution of CN at the slit diaphragm. Physiol Rep 2016; DOI:10.14814/phy2.12679.
4 Nourbakhsh N, Mak RH: Steroid-resistant nephrotic syndrome: past and current perspectives. Pediatric Health Med Ther 2017;8:29-37.
5 Brooks C, Wei Q, Cho SG, Dong Z: Regulation of mitochondrial dynamics in acute kidney injury in cell culture and rodent models. J Clin Invest 2009;119:1275-1285.
6 Frank S, Gaume B, Bergmann-Leitner, Leitner WW, Robert EG, Catez F, Smith CL, Youle RJ: The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis. Dev Cell 2001;1:515-525.
7 Park J, Choi H, Min J S, Kim B, Lee SR, Yun JW, Choi MS, Chang KT, Lee DS: Loss of mitofusin 2 links beta-amyloid-mediated mitochondrial fragmentation and Cdk5-induced oxidative stress in neuron cells. J Neurochem 2015;132:687-702.
8 Qadhi R, Alsaleh N, Samokhvalov V, El-Sikhry H, Bellenger J, Seubert JM: Differential responses to docosahexaenoic acid in primary and immortalized cardiac cells. Toxicol Lett 2013;219:288-297.
9 Hom J, Sheu SS: Morphological dynamics of mitochondria-a special emphasis on cardiac muscle cells. J Mol Cell Cardiol 2009;46:811-820.
10 Suzanne Hoppins, Laura Lackner, Jodi Nunnari: The Machines that divide and fuse mitochondria. Annu Rev Biochem 2007;76:751-780.
11 Kanfer G, Kornmann B: Dynamics of the mitochondrial network during mitosis. Biochem Soc Trans 2016;44:510-516.
12 Chang CR, Blackstone C: Dynamic regulation of mitochondrial fission through modification of the dynamin-related protein Drp1. Ann N Y Acad Sci 2010;1201:34-39.
13 Taguchi N, Ishihara N, Jofuku A, Oka T, Mihara K: Mitotic phosphorylation of dynamin-related GTPase Drp1 participates in mitochondrial fission. J Biol Chem 2007;282:11521-11529.
14 Chang CR, Blackstone C: Cyclic AMP-dependent protein kinase phosphorylation of Drp1 regulates its GTPase activity and mitochondrial morphology. J Biol Chem 2007;282:21583-21587.
15 Guan N, Ren YL, Liu XY, Zhang Y, Pei P, Zhu SN, Fan Q: Protective role of cyclosporine A and minocycline on mitochondrial disequilibrium-related podocyte injury and proteinuria occurrence induced by Adriamycin. Nephrol Dial Transplant 2015;30:957-969.
16 Liu X, Liu Y, Yang Y, Xu J, Dai D, Yan C, Li X, Tang R, Yu C, Ren H: Antioxidative Stress Effects of Salvia przewalskii Extract in Experimentally Injured Podocytes. Nephron 2016;134:253-271.
17 Xu S, Nam SM, Kim JH, Das R, Choi SK, Nguyen TT, Quan X, Choi SJ, Chung CH, Lee EY, Lee IK, Wiederkehr A, Wollheim CB, Cha SK, Park KS: Palmitate induces ER calcium depletion and apoptosis in mouse podocytes subsequent to mitochondrial oxidative stress. Cell Death Dis 2015;6:e1976.
18 Wei Q, Liu X, Wu G, Wu H, Zhu S, Guan N: Mitochondrial fission proteins are involved in proteinuria in adriamycin-induced rat nephropathy. J Nephrol Dialy Transplant 2017; DOI:10.3969/cndt.j.issn.1006-298X.2017.01.007 (Chinese).
19 de Arriba G, Calvino M, Benito S, Parra T: Cyclosporine A-induced apoptosis in renal tubular cells is related to oxidative damage and mitochondrial fission. Toxicol Lett 2013;218:30-38.
20 Nigro M, De Sanctis C, Formisano P, Stanzione R, Forte M, Capasso G, Gigliotti G, Rubattu S, Viggiano D: Cellular and subcellular localization of uncoupling protein 2 in the human kidney. J Mol Histol 2018; DOI:10.1007/s10735-018-9782-3.

21 Pozdzik A, Brochériou I, David C, Touzani F, Goujon JM, Wissing KM: Membranous Nephropathy and Anti-Podocytes Antibodies: Implications for the Diagnostic Workup and Disease Management. Biomed Res Int 2018;2018:6281054.
22 Wang L, Nomura M: Loss of Drp1 in the liver leads to an alteration in expression of the genes involved in the immune system. Genom Data 2015;6:27-30.
23 Baixauli F, Martín-Cófreces NB, Morlino G, Carrasco YR, Calabia-Linares C, Veiga E, Serrador JM, Sánchez-Madrid F: The mitochondrial fission factor dynamin-related protein 1 modulates T-cell receptor signaling at the immune synapse. EMBO J 2011;30:1238-1250.
24 Shahni R, Cale CM, Anderson G, Osellame LD, Hambleton S, Jacques TS, Wedatilake Y, Taanman JW, Chan E, Qasim W, Plagnol V, Chalasani A, Duchen MR, Gilmour KC, Rahman S: Signal transducer and activator of transcription 2 deficiency is a novel disorder of mitochondrial fission. Brain 2015;138:2834-2846.
25 Wilson TJ, Slupe AM, Strack S: Cell signaling and mitochondrial dynamics: Implications for neuronal function and neurodegenerative disease. Neurobiol Dis 2013;51:13-26.