

アジア太平洋腎研究推進室ニュース

高雄東京腎臓病研究会（16th Kaohsiung-Tokyo Nephrology Conference）が10月20日（火）台湾の高雄医学大学で開催されました。この研究会は、高雄医学大学腎臓内科と順天堂大学腎臓内科が年1回交互に担当し、腎臓病に関する基礎・臨床研究について討論しているもので、優れた内容は国際雑誌に投稿してきました。若手の研究者・医師にとっては、英語力を高めると同時に友情を深める良い機会となっています。松和会田無クリニックの福井光峰院長が高雄医学大学の卒業ということもあり、当研究推進室から二名参加させていただきました。古くからの友人と意見交換を行い、大変楽しいひと時でした。

（アジア太平洋腎研究推進室長 富野康日己）

第十六屆高雄東京腎臓病研討會

Sixteenth Kaohsiung-Tokyo Nephrology Conference



Time: October 20, 2015

Place: first Meeting Room, 6th Floor (Tuesday),
Chung-Ho Memorial Hospital,
Kaohsiung Medical University,
Kaohsiung, Taiwan.

主辦:高雄醫學大學附設醫院腎臓内科、高雄市立旗津醫院

協辦:蔡瑞熊健康關懷文教基金會

Program

October 20, 2015

14:00-14:10 Opening
Yasuhiko Tomino

Prof. Hung-Chun Chen,

Chairman: Dr. Teruo Hidaka & Yi-Wen Chiu

Time	Topic	Speaker
14:10-14:40	Risk Factors Associated with Mammalian Target of Rapamycin Inhibitors Withdrawal in Kidney Transplant Recipients	Lee Moay Lim
14:40-15:10	The low opsonization and immune complexes solubilization ability in sera from patients with hereditary angioedema (HAE)	Daisuke Honda
15:10-15:40	Abnormal global glomerular sclerosis rate in remnant kidney of ipsilateral nephroureterectomy is associated with higher risk of end-stage renal disease within five years in patients of upper urinary tract urothelial carcinoma, a retrospective cohort study	Shengwen Niu

15:40-16:00 Coffee break

Chairman: Dr. Yusuke Suzuki & Jer-Ming Chang

Time	Topic	Speaker
16:00-16:30	Reduced responsiveness to the actions of Transforming Growth Factor- β and induced anti-apoptosis in RAGE knock out mesangial cells	Shinji Hagiwara
16:30-17:00	De novo Mutation in the ADPKD	Daw-Yang Hwang
17:00-17:30	Podocin is translocated to cytoplasm in injured podocyte such as puromycin aminonucleoside nephrosis rats model and poor-prognosis patients with IgA nephropathy	Teruo Hidaka

17:30-17:40 Closing

Prof. Hung-Chun Chen

Risk Factors Associated with Mammalian Target of Rapamycin Inhibitors Withdrawal in Kidney Transplant Recipients

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Introduction

Mammalian Target of Rapamycin Inhibitors (MTORi) have essential role as novel immunosuppressive agent in kidney transplantation. With its antiproliferative and antineoplastic properties, MTORi potentially have important long-term therapeutic consideration since cardiovascular disease and malignancy are important concern after kidney transplantation. However, treatment cessation frequently occurs following its unique adverse effects. The risk factors associated to MTORi withdrawal is largely unclear. The objective of this study was to investigate the impacts of MTORi withdrawal on transplant outcomes and the risk factors for MTORi withdrawal in kidney transplant recipient.

Material and methods

This retrospective observational study population consisted of kidney transplant recipients followed up in a medical center in Southern Taiwan from January 1999 till December 2014. The baseline characteristic and transplantation related profiles were collected by the time of enrollment. The impacts of MTORi withdrawal on renal transplant outcomes (graft survival, patient survival, and new onset diabetes mellitus [NODM]) were investigated using multivariate Cox regression and logistic regression analysis. We further examined the risk factor for MTORi withdrawal using multivariate logistic regression analysis. $P < 0.05$ was considered as statistically significant.

Results

A total of 77 kidney transplant recipients who received MTORi treatments were included, with 28 patients withdrew (36.3%). MTORi withdrawal was associated with an increased risk of graft failure [adjusted HR=9.97, $P=0.047$]. However, it was not significantly associated the risk for mortality (adjusted HR=0.98, $P=0.98$). MTORi withdrawal was associated with an increased risk for NODM in the univariate analysis (HR=5.86, $P=0.008$); Nevertheless, it was not statistically significant after adjusting for other risk factors (HR=4.56, $P=0.08$). The risk factors for mTORi withdrawal included initial proteinuria (adjusted OR= 7.48, $P=0.009$), higher initial serum creatinine (per 1 mg/dl increment, adjusted OR=3.66, $P=0.04$), and glomerulonephritis as primary renal disease (adjusted OR=8.62, $P=0.02$).

Conclusion

MTORi withdrawal is a strong risk factor for renal graft failure. Proteinuria, poor initial graft function and primary renal disease of glomerulonephritis are predictors for MTORi withdrawal. Earlier identification of these risk factors may assist physician to decide the best candidate for MTORi conversion in order to optimize transplantation outcomes.

The low opsonization and immune complexes solubilization ability in sera from patients with hereditary angioedema (HAE)

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Background: Hereditary angioedema (HAE) is a rare autosomal dominant disease caused by C1 inhibitor dysfunction. As some serum complement factors are continuously consumed in HAE, patients may have poor opsonization and immune complexes (IC) solubilization ability. Generally the presentation of such symptoms would be considered a sign of autoimmune disorders, in fact, it has been reported that a lot of HAE patients present autoimmune disorders. In the present study, we aimed to clarify the pathological mechanisms that lay behind the appearance of autoimmune disorders in patients with HAE by making a comparison of the opsonization and IC solubilization ability of HAE serum with that of healthy control serum.

Patients and Methods: All 18 HAE patients (male:female, 8:10) who had been diagnosed in our department were enrolled. The serum samples were obtained from HAE patients in stable condition and normal volunteers. Apoptotic cells were co-cultured under serum with macrophages. The rate of phagocytosis per hundred macrophages was evaluated as an indicator of the opsonization ability. Moreover, IC made by peroxidase and anti-peroxidase antibody and serum were mixed. The free peroxidase in the supernatant was then quantified and used as an indicator of the IC solubilization ability.

Results: The average age of HAE patients was 46.7 years old. Twelve patients showed some autoimmune disorder findings, such as a decrease in C1q level, an increase of IC, a false positive reaction of cryoprecipitate, and/or a positive reaction of anti-nuclear antibody. The opsonization ability in normal human serum (NHS) was about 70 %, but was around 20 % in HAE serum. In addition, that ability recovered in NHS added to HAE serum. The ability was inhibited after adding anti-complement receptor (CR) 1, 3, and 4 antibodies. C1q, C4d, and iC3b were detected on the apoptotic cells by flow cytometry, but the amounts of these deposits with HAE serum were lower than that with NHS. Furthermore, the IC solubilization ability in HAE serum was much lower than that in NHS.

Conclusion: The low level of early complement components in patients with HAE might induce autoimmune disorder findings.

Abnormal global glomerular sclerosis rate in remnant kidney of ipsilateral nephroureterectomy is associated with higher risk of end-stage renal disease within five years in patients of upper urinary tract urothelial carcinoma, a retrospective cohort study

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Background: Patients of upper urinary tract urothelial carcinoma (UTUC) post unilateral nephrectomy have higher risk into dialysis than those of renal cell carcinoma. However, we don't know if UTUC itself has impact on renal outcome. We studied the pathological changes of remnant kidney tissue from UTUC patients post ipsilateral nephroureterectomy to investigate the correlation between renal histopathology and outcome of end-stage renal disease.

Hypothesis: The renal histopathologic changes in remnant kidney of ipsilateral nephroureterectomy are associated with renal survival rate in UTUC patients.

Method and Material: This cohort study included 132 cases of non-dialysis UTUC patients post ipsilateral nephroureterectomy from 2002 to 2010. We collected clinical and laboratory data before surgery, tumor size, whether into dialysis after surgery, and followed up to dialysis or to December 31, 2014. Renal histopathology was read by 3 specialists: nephrologists or pathologist. We used logistic regression for studying tubulointerstitial fibrosis score and global glomerular sclerosis (GGS) rates and Cox regression to investigate factors associated with renal survival rate.

Results: There was no significant factor associated with tubulointerstitial fibrosis, but advanced chronic kidney disease was significantly related to GGS rate adjusted with age and gender [OR (95%CI): 4.8 (1.4-16.9), p=0.014]. Kaplan-Meier survival curve showed five-year renal survival rate was 86.3%. Factors affected five-year renal survival included hypertension [HR (95%CI): 4.0 (1.1-15.2), p=0.043] and GGS rate [HR (95%CI): 17.4 (2.4-124.1), p=0.004].

Conclusion: Our findings demonstrated that UTUC patients with hypertension before surgery or abnormal GGS rate in remnant kidney have higher risk of entering dialysis within five years post ipsilateral nephroureterectomy.

Key words: upper urothelial tract urothelial cancer, end-stage renal disease, tubulointerstitial fibrosis, glomerular sclerosis rate

Reduced responsiveness to the actions of Transforming Growth Factor- β and induced anti-apoptosis in RAGE knock out mesangial cells

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Background: As it has been shown that genetic deletion of RAGE improved albuminuria and glomerular sclerosis in diabetic mouse kidney, the ligation of advanced glycation end products (AGEs) to their receptor (RAGE) activates multiple intracellular signaling pathways and leads to development of diabetic nephropathy.

Methods: We analysed the expression of mRNAs and proteins related to fibrosis and inflammation from RAGE KO mesangial cells (MCs) under conditions of low and high glucose, in the presence or absence of TGF- β .

Results: Bioinformatic analysis of RNA-seq data from MCs from RAGE KO mice revealed decreased TGF- β responsiveness of signaling pathways involved in cholesterol biosynthesis, extracellular matrix organization, collagen formation and apoptosis compared to WT MCs. Interestingly, several profibrotic, proinflammatory and cell proliferation markers were upregulated in RAGE KO compared to wild type MCs at baseline. S100A4, also known as FSP1, was remarkably up-regulated in RAGE KO MCs. Furthermore, RAGE KO MCs have a more proliferative phenotype and exhibit less apoptosis properties that are contributed to at least in part by up-regulation of S100A4 in these cells.

Conclusions: RAGE KO mesangial cells exhibited reduced responsiveness to the actions of TGF- β and anti-apoptotic phenotype.

De novo Mutation in the ADPKD

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PKD1 and PKD2 are known to be highly mutable genes, and many ADPKD families have their own unique mutation. Clinical diagnosis of ADPKD depends heavily on the family history, and lacking of positive family history can cause difficulty in the diagnosis.

A 35 years old male without family history of kidney disease was diagnosed of polycystic kidney disease in the high school and received renal replacement therapy at the age of 30 years old. Genetics analysis of PKD1 and PKD2 was performed and two PKD1 mutations were identified as p.Ser1457fs (c.4369_4370delTC) and p.C259Y (c.776G>A). These two mutations were listed as definitely disease-causing and highly pathogenic in the Mayo Clinic PKD Database, respectively. Whole exome sequencing was performed in the patient and no other known kidney cystic disease genes were found. Mutation p.Ser1457fs was not found in both parents, indicating the de novo nature of this mutation. Interestingly, patient's father and one of the sisters have p.C259Y mutation but clinically their kidney function is normal. Few renal cysts were identified in the father while no apparent renal cyst in the sister.

Our study suggests the PKD1 p.C259Y is a hypomorphic mutation and will not lead to ADPKD per se. However, a combination of p.C259Y and p.Ser1457fs cause a severe ADPKD phenotype. This result indicates the diagnosis of ADPKD is complex and de novo mutation, the combination effects of 2 mutations, and the potential flaw in the database must be considered.

Podocin is translocated to cytoplasm in injured podocyte such as puromycin aminonucleoside nephrosis rats model and poor-prognosis patients with IgA nephropathy

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Background: Podocytes is highly differentiated cells and serve as the final barrier to urinary protein loss through a specialized structure. Podocyte injury results in progressive glomerular damage and accelerates sclerotic changes, although the exact mechanism of podocyte injury is still obscure. We focus on the staining gap (podocin gap) defined as the staining difference between podocin and synaptopodin, which are normally located in the foot process.

Results: In puromycin aminonucleoside nephrosis (PAN) rats, the podocin gap is significantly increased ($p<0.05$) and podocin is translocated to the cytoplasm on days 7 and 14 but not on day 28. Surprisingly, the gap is also significantly increased ($p<0.05$) in human kidney biopsy specimens of poor-prognosis IgA nephropathy patients. This suggests that the podocin gap indicates the translocation of podocin to the cytoplasm and could be a useful marker for classifying the prognosis of IgA nephropathy. Next, we find more evidence of podocin trafficking in podocytes where podocin merges with Rab5 in PAN rats at day 14. In immune-electron microscopy, the podocin positive area was significantly translocated from the foot process areas to the cytoplasm ($p<0.05$) on days 7 and 14 in PAN rats. Interestingly, podocin is also translocated to the cytoplasm in poor-prognosis human IgA nephropathy.

Conclusion: We demonstrate that the translocation of podocin by endocytosis could be a key traffic event of critical podocyte injury and that the podocin gap could indicate the prognosis of IgA nephropathy.

Keywords: Podocyte; Podocin; Synaptopodin; IgA nephropathy; Puromycin aminonucleoside nephrosis rats