

Department of Internal Medicine

Division of Nephrology and Hypertension

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General Summary

Our department is one of the largest nephrology departments in Japan and includes all subspecialties of nephrology, i.e., from early chronic kidney disease (CKD) with proteinuria to dialysis and kidney transplantation. Therefore, our research groups are investigating diverse subjects and aim to eventually find new therapeutic strategies and mechanisms of disease progression, which may help decrease the number of patients with end-stage renal diseases.

Research Activities

Studies of immunoglobulin A nephropathy

We demonstrated that tonsillectomy and histological grade indicate a lower risk of recurrence in patients with immunoglobulin A (IgA) nephropathy. Studies have been published of patients with IgA nephropathy showing acute exacerbations after long-term courses and the analysis of elderly patients with IgA nephropathy.

Studies of low glomerular density in CKD

Our studies showed that low glomerular density was strongly associated with the prognosis of various diseases. Collaborative research about the estimation of nephron numbers in Japanese is in progress.

Studies on podocyte damage

Transgenic mice (NEP25) express human CD25 (hCD25) selectively on podocytes, and injection of hCD25-targeted recombinant immunotoxin permits selective injury only to podocytes. We generated mosaic mice that contain both hCD25⁺ and hCD25⁻ podocytes. The immunotoxin sequentially induced hCD25⁻ podocyte injury, and this effect was dominant, especially in male mice.

Basic study of kidney regeneration

We demonstrated the construction of urine excretion pathways in rats. Rat metanephroi or metanephroi with bladders (developed from cloacas) were transplanted into host rats. Histopathologic analysis showed that tubular lumina dilation and interstitial fibrosis were less common in kidneys developed from cloacal transplantation than in kidneys developed with metanephroi transplantation. We then connected the host animal's ureter to the cloa-

cal-developed bladder, a technique we called the stepwise peristaltic ureter (SWPU) system. The application of the SWPU system avoided hydronephrosis and permitted the cloacas to differentiate well, with cloacal urine being excreted persistently through the recipient ureter. Finally, we demonstrated a viable preclinical application of the SWPU system in cloned pigs. In the pig study the SWPU system also inhibited hydronephrosis.

Studies of CKD mineral and bone disorder

We investigated the epigenetic modifications in the parathyroid glands of CKD-mineral and bone disorder, then we have reported modifying DNA methylation patterns in parathyroid glands with CKD-mineral and bone disorder. We then analyzed the glial cells missing homolog 2 gene (*Gcm2*) in parathyroid glands, which is the essential transcription factor for parathyroid development in terrestrial vertebrates. Furthermore, we conduct a biological functional analysis of *Gcm1*, an ortholog of *Gcm2*, in the kidney. The magnesium concentration is a proven predictor of mortality in hemodialysis patients. We showed in a prospective cohort study that the use of a proton pump inhibitor is associated with an increased risk of hypomagnesemia in patients with hemodialysis. To clarify the association between all-cause mortality and the magnesium concentration, including fibroblast growth factor 23, we are now conducting a cohort study. Using annual surveys of dialysis facilities throughout Japan managed by the Japanese Society for Dialysis Therapy we have also identified the associations between higher serum ferritin levels and higher rates of all-cause and cardiovascular mortality among 191,902 patients who are undergoing hemodialysis and peritoneal dialysis.

Studies of peritoneal dialysis

With outcomes of combined therapy with peritoneal dialysis and hemodialysis in a cohort of more than 100 patients we confirmed the availability of combined therapy. Moreover, we found that the survival outcome with combined therapy was not worse than that with peritoneal dialysis or hemodialysis alone. We are using laparoscopy to evaluate peritoneal injury.

Study of renal transplantation

We participated in the Japan Academic Consortium of Kidney Transplantation and investigated Alport syndrome and IgA vasculitis in patients with kidney transplantation. We found that Alport syndrome did not recur and that the rates of allograft and patient survival were similar to those of other diseases. In cases of IgA vasculitis, we found that the recurrence rate was 28.6% and that recurrence itself did not affect allograft survival. This result could be an effect of tonsillectomy plus corticosteroid pulse therapy. In addition, we found that the single nucleotide polymorphism of the glucocorticoid induced 1 gene (*GLCCI1*) could be related to posttransplant hypertension.

Renal protective effects of T-type calcium channel blockade via the blood-brain barrier in CKD model rats

We investigated whether the mechanism of a renal protective effect differs because of an agent's ability to penetrate the blood-brain barrier. A new T-type calcium channel

blocker, which can or cannot penetrate the blood-brain barrier, was examined.

Renal protective effects of azilsartan in a rat model of adenine-induced renal failure

Although daily urinary sodium excretion was decreased in nonmedicated rats, azilsartan lead to fewer decreases in sodium excretion, urinary protein excretion, and sympathetic nerve activity. We will investigate the molecular mechanism of the renal protective effects by the suppression of sympathetic nerve activity.

A lower serum level of uric acid is associated with rates of all-cause and cardiovascular mortality among patients receiving hemodialysis in Japan

We investigated the relationship of the serum level of uric acid to the rates all-cause and cardiovascular mortality in patients receiving hemodialysis. Lower serum levels of uric acid were independently associated with the rates of all-cause and cardiovascular mortality among patients receiving hemodialysis. A close monitoring of the serum level of uric acid is believed to be necessary to assess patients receiving hemodialysis.

Publications

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