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 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
A multicenter, prospective cohort study, the Japan IgA Nephropathy Cohort Study, is currently in progress. The study will validate the effectiveness of a series of therapeutic regimens, including tonsillectomy or corticosteroid therapy or both, which are widely accepted in Japan. A post-hoc analysis of retrospective multicenter large-scale study is in progress to validate treatments for advanced cases of immunoglobulin A nephropathy when diagnosed at biopsy.

Studies of total nephron number counting
We have performed a study of stereology-based total nephron number (TNN) counting using kidneys obtained at autopsy from Japanese subjects. The study revealed that the TNN in Japanese subjects is one of the lowest nephron counts yet reported. Through the combined use of computed tomography imaging and biopsy specimens, a study to examine TNN in clinical settings is in progress.

In vivo regeneration of interspecies chimeric kidneys using a nephron progenitor cell replacement system
Kidney regeneration is expected to be a new alternative treatment to the currently limited treatments for chronic kidney disease. By transplanting exogeneous nephron progenitor cells (NPCs) into the metanephric mesenchyme of a xenogeneic fetus, we aimed to regenerate neo-kidneys that originate from transplanted NPCs. Previously, we generated a transgenic mouse model (the Six2-iDTR mouse) enabling drug-induced ablation of NPCs. We demonstrated that eliminating existing native host NPCs allowed their 100% replacement with donor mouse or rat NPCs, which could generate neo-nephrons on a cul-

ture dish. To apply this method to humans in the future, we examined the possibility of the in vivo regeneration of nephrons between different species via NPC replacement. We injected NPCs-containing rat renal progenitor cells and diphtheria toxin below the renal capsule of E13.5 metanephroi of Six2-iDTR mice; the injected metanephroi were then transplanted into recipient rats treated with immunosuppressants. Consequently, we successfully regenerated rat/mouse chimeric kidneys in recipient rats receiving the optimal immunosuppressive therapy. We revealed a functional connection between the neo-glomeruli and host vessels and proper neo-glomeruli filtration. In conclusion, we successfully regenerated *in vivo* interspecies kidneys that acquired a vascular system. This novel strategy might represent an effective method for human kidney regeneration.

Studies of CKD mineral and bone disorder

We previously reported that the DNA methylation patterns in calcium sensing receptor gene (*CASR*) and the vitamin D receptor gene (*VDR*) were modified in the parathyroid glands (PTGs) of CKD-mineral and bone disorder (MBD) and that the glial cells missing transcription factor 2 gene (*GCM2*) plays an essential role in adult PTG cell proliferation and maintenance. Furthermore, we are investigating how the CKD environment and a high-phosphorus diet affects early changes in gene expression and cell cycle acceleration in PTGs. Because glycometabolism is attracting the most attention in various fields, we then investigated insulin resistance in patients with CKD. As a result, we elucidated the association between insulin resistance and *fibroblast growth factor 23* (*FGF23*) in patients with CKD (Scientific Reports 2018). To clarify the association insulin resistance and all-cause mortality, cardiovascular events, and CKD-MBD in patients undergoing hemodialysis, we are performing a conduct cohort study. In addition, because vascular calcification is the main cause of cardiovascular disease events in patients with CKD, establishing a treatment strategy is important. We are investigating the association between vascular calcification and CKD-MBD, especially magnesium, in patients with CKD. Our purpose is to prevent and regress vascular calcification.

Study of renal transplantation

We participated in the Japan Academic Consortium of Kidney Transplantation, which is composed of Tokyo Women's Medical University and Kyushu University and now continue to investigate hyperuricemia and diabetic nephropathy. In our single center analysis, we investigated the association between donor fibroblast and posttransplant anemia, and the following themes are currently in progress: (1) denervation, (2) the effect of tonsillectomy for immunoglobulin A nephropathy, and (3) endoplasmic reticulum stress. As for basic science *in vivo*, we established rat kidney transplant models and analyzed renal endothelial cell transformation and the role of pericyte in kidney fibrosis.

Studies of peritoneal dialysis

We reported that the prevalence of peritoneal dialysis (PD)-associated peritonitis and outcome including patient survival and technical survival were not significantly different between patients who had or did not have diabetes while undergoing PD. We reported that the lipid profile was associated with the deterioration of residual renal function in incident

PD patients. We conduct clinical research on the bicarbonate/lactate-buffered neutral PD solution, the clinical efficiency of incremental PD, the management for PD-associated peritonitis, and pathologic changes of the peritoneal membrane. Additionally, we started to use a new ultrafine laparoscope to evaluate peritoneal injury.

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

We are investigating the mechanism for differences in an agent's capacity to penetrate the blood-brain barrier by examining new T-type calcium channel blocker agents that can or cannot penetrate the blood-brain barrier.

Relationship between clinical character of primary aldosteronism and hormone kinetics of the renin-angiotensin system

For simplicity diagnosis and decision of method of treatment for primary aldosteronism (PA), we evaluated with various criteria the characteristics of patients with positive results of the captopril challenge test. We also evaluated the relationship between clinical characteristics of PA and the results of various confirmatory tests or adrenal venous sampling. We are evaluating with several plasma markers the reactiveness to medications for treating PA.

Publications

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