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 on IgA nephropathy (IgAN)
A multicenter, prospective cohort study (J-IGACS) is currently in progress. The study will validate the effectiveness on a series of therapeutic regimens, including tonsillectomy and/or corticosteroid therapy, which is widely accepted in Japan. The post-hoc analysis of retrospective multicenter large-scale study is under progress for the validation of therapeutic interventions in advanced IgAN cases at the time of biopsy diagnosis.

Studies on total nephron number counting
We have performed a stereology-based total nephron number (TNN) counting using autopsy kidneys in Japanese subjects. The study revealed that the TNN in Japanese subjects is one of the lowest nephron counts yet reported. By the combination use of image study and biopsy specimen, a study to examine TNN in clinically available settings is currently under progress.

Study of renal transplantation
We participated in Japan Academic Consortium of Kidney Transplantation (JACK) and published the following clinical and pathological analysis focused on;1. Alport syndrome, 2. De novo membranous nephropathy. We also published the significance of GLCCI-1 SNIP on hypertension after kidney allograft recipients and clinical and pathological features of plasma cell rich rejection and diabetic nephropathy. The following theme about kidney transplantation are currently in progress; 1. Diabetic nephropathy 2. Hyperuricemia, 3. Post transplant anemia, 4. The prognostic value of pathological findings in donor baseline biopsy and 5. Endoplasmic reticulum stress. Regarding basic science in vivo, we established rat kidney transplant model and analyze the renal endothelial cells transforma-

tion. We also investigate the role of pericyte in rat kidney injury model. The extracellular matrix in cultured endothelial cells in vitro are also investigated.

Studies of CKD-MBD
We previously reported that the DNA methylation patterns in CaSR and VDR genes were modified in the parathyroid glands (PTGs) of chronic kidney disease-mineral and bone disorder (CKD-MBD). We then analyze the effect of histone modification and cell cycle in the PTGs of CKD-MBD. Furthermore, we are investigating how glial cells missing 2 (Gcm2) in PTGs, which is the essential transcription factor for parathyroid development in terrestrial vertebrates, affects PTGs function. In addition, we conduct a biological functional analysis of Gcm2 ortholog, Gcm1 in the kidney.

Renal protective effects of T-type calcium channel blockade via blood brain barrier in chronic kidney disease model rats
We are evaluating the mechanism of renal protective effect by the suppression of sympathetic nerve by T-type calcium channel blocker (T-CCB). We investigate the mechanism via the agent's difference from capacity of penetrating the blood-brain barrier, using the new T-CCB agent, which can or cannot penetrate the blood-brain barrier.

Renal protective effects of azilsartan in adenine-induced renal failure model rats
Although daily urinary sodium excretion is decreased in non-medication group, azilsartan (Azi) suppressed the decreasing sodium excretion, urinary protein excretion and sympathetic nerve activity. We revealed that one of the molecular mechanism of renal protection by Azi is the effect for natrium transporter.

Basic study for kidney regeneration
A novel system to regenerate the kidney by replacing nephron progenitor cells in an empty niche.
The kidneys develop through reciprocal and sequential interactions between the ureteric bud (UB) and surrounding cap mesenchyme (CM). The engraftment efficiency of cells transplanted to a nephrogenic niche has been very low, with the underlying cause considered to be the competition with the existing native host cells occupying the niche.
We demonstrated that the transplanted progenitor cells replaced the native progenitor cells in CM using a nephron progenitor eliminate system that used Cre-LoxP technology in combination with diphtheria toxin (DT)-mediated cell elimination.
Using the progenitor eliminate system, it was shown that competing native progenitor cells were completely replaced by transplant cells in CM. Furthermore, the replaced transplant cells displayed reciprocal interactions with the host UB and complete differentiation to nephrons.
Next, we determine the optimal administration route and dose of DT. Two DT administration routes (intra-peritoneal and intra-amniotic injection) were evaluated in fetal mice. The intra-peritoneal route was not sufficient for NPC elimination. By establishing that intra-amniotic injection is the optimal administration route for DT, these results will facilitate studies of kidney regeneration in vivo. In addition, this method might be useful

for analysis of kidney development at various time points by deleting NPCs during development.

Publications

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