Results: Patients in the highest tertile of serum free IS showed shorter dialysis vintage and higher body weight compared to dialysis sessions than patients in the other two tertiles. Patients in the highest tertile of IS showed lower body weight and serum concentrations of alkaline phosphatase, 1, 25(OH)2D and PTH compared to the lowest tertile. No relationships of serum free CS concentrations with phosphate and calcium metabolism variables were observed. Kaplan-Meier survival analysis shows an increased cardiovascular morbidity in patients in the CS highest tertile (blue line in the figure) compared to those in the lowest and middle tertiles taken together (red line; p = 0.01). This association was not found considering IS tertiles.

Conclusions: Our findings suggest that serum IS could predispose to adynamic bone disease, while CS may have higher cardiovascular toxicity.

PO0609

Rac1 Promotes Kidney Collecting Duct Integrity by Limiting Actomyosin Activity

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Background: A polarized collecting duct (CD) is critical for an intact kidney. The branched kidney collecting system is formed from the ureteric bud (UB). This requires a dynamic actin cytoskeleton and balanced actomyosin activity allowing normal tissue polarization, morphology and function. The small Rho GTTase, Rac1, is a key molecular switch that controls actin polymerization and branching. We investigated the role of Rac1 in kidney collecting system morphogenesis by selectively deleting it in mice at the initiation of UB development.

Methods: We crossed Rac1flox/flox (f/f) with Hoxb7-cre deleting Rac1 in the ureteric bud starting at E10.5 and followed kidney development throughout adulthood. We also analyzed the role of Rac1 in regulating signaling, migration, spreading, tubulogenesis and polarity by utilizing primary inner medullary collecting duct Rac1 null cells.

Results: The kidneys of Hoxb7:Rac1f/f exhibited only a mild branching morphogenesis defect as Rac1 is expressed after most UB branching is complete. However, with aging the CD developed a disruption of epithelial integrity, resulting in fibrosis, and a urine concentration defect. Despite intact integrin signaling, Rac1 null CD cells had profound spreading, adhesion and polarity abnormalities that were independent of the major downstream Rac1 effector, Pak1. Instead, Rac1 null cells demonstrated defective WAVE2-Arp2/3 dependent actin cytoskeletal branching which resulted in excessive actomyosin activity and severe abnormalities in epithelial cell shape. The functional and morphological defects caused by Rac1 deficiency were reversed by direct myosin II inhibition using low dose blebbistatin.

Conclusions: Unexpectedly, Rac1 does not play a major role in early branching morphogenesis of the renal collecting system, however it is required for adult CD integrity. Mechanistically, Rac1 controls Arp2/3-dependent cytoskeletal branching which limits actomyosin hyperactivity allowing normal epithelial polarization, function and morphology.

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PO0610

Stromal Transcription Factor 21 Is Critical for Development of the Interstitium and Neprhon Progenitor Cells Via Interaction with Wnt/β-Catenin Signaling

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Background: Reciprocal signaling between the collecting duct progenitors and the nephron progenitor cells (NPC) is the primary driver for kidney development. In addition, recent studies implicate input from the interstitial progenitor cells in multiple aspects of kidney development. However, the mode of interstitial cell action on kidney development is poorly understood. We previously showed that the Transcription factor 21 (Tcf21) in interstitial progenitors is required for normal ureteric bud branching. Here, we examined roles for Tcf21 in renal interstitial progenitors in mediating stromal functions during kidney development.

Methods: Stromal Tcf21 was evaluated with the Foxd1Cre;Tcf21f/f mouse model by standard immunohistological analyses. MK3 and M15 metanephric mesenchymal cell lines were used for analyses of β-catenin signaling.

Results: In the Foxd1Cre;Tcf21f/f kidney, absence of Tcf21 from Foxd1+ stromal progenitors caused decrease in stromal cell proliferation, leading to marked reduction of the medullary stromal space. Lack of Tcf21 in Foxd1 stromal cells also led to defective differentiation to perivascular cells and mesangial cells. Non-autonomously, absence of stromal Tcf21 led to expansion of the Six2+ NPC, suggestive of delayed NPC differentiation, and to poor development of the Loop of Henle and the collecting ducts. We next examined whether Tcf21 modulates Wnt/β-catenin signaling. Significantly less β-catenin was observed in stroma of the Foxd1Cre;Tcf21f/f mouse compared to their wild-type littermates. In MK3 and M15 cells, stabilization of β-catenin by Lithium Chloride upregulated Tcf21 expression, while over-expression of Tcf21 enhanced expression of Wnt-target genes upon β-catenin stabilization. Further, Tcf21 enhanced TCF/LEF reporter