Methods: After sham or unilateral ureteral obstruction (UUO) operation, 20-25 g male C57BL/6 mice were treated with vehicle or SAC (10 mg/kg) for 14 days. Moreover, normal rat kidney interstitial fibroblasts (NRK-49F) were treated with various concentrations of SAC (10 nM to 100 nM). Protein samples from in vivo and in vitro experiments were collected to assess renal fibrosis.

Results: Treatment with SAC reduced the deposition of interstitial matrix proteins in UUO kidneys as shown by Masson staining. The expression of Fibronectin, collagen-I and α-smooth muscle actin (α-SMA) were increased in UUO-induced fibrotic kidneys, which were down-regulated in SAC treated UUO kidneys. In parallel, treatment with SAC reduced gene expression of fibronectin and collagen-I in NRK-49F cells. RNA sequencing analysis showed that multiple genes belong to the PPAR (peroxisome proliferator-activated receptor) signaling pathway were up-regulated by SAC treatment in UUO kidneys.

Conclusions: SAC inhibits renal fibrosis in obstructed kidneys possibly through activation of the PPAR signaling pathway.

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PUB326

Role of PAR-1 in Immune Activation and Tubulointerstitial Fibrosis During AKI-to-CKD transition
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Background: The high-affinity thrombin receptor protease-activated receptor-1 (PAR-1) has been recognized as a therapeutic target for cardiovascular intervention. Emerging evidence suggests that the coagulation cascade is activated in the kidney interstitium during AKI. Yet, the role of PAR-1 signaling in AKI to CKD transition remains largely unexplored.

Methods: We investigated the effect of PAR-1 deficiency in a longitudinal kidney fibrotic murine AKI to CKD transition model. PAR-1−/− and wild type mice underwent unilateral ischemia-reperfusion injury (UIRI) for 7, 14 and 28 days. Uninephrectomy of the contralateral kidney was performed one day before sacrifice to assess renal injury.

Results: After 14 or 28 days of UIRI, BUN was significantly lower in PAR-1−/− vs wild type mice. PAR-1−/− mice showed diminished kidney fibrosis with reduced ECM accumulation and expression of fibronectin, α-smooth muscle actin and collagen via TGF-β/Smad signaling after UIRI. Macrophage infiltration and inflammation was alleviated in PAR-1−/− ischemic kidneys in which macrophage M1-polarization and its secretory cytokine TNF-α were attenuated.

Conclusions: PAR-1 deficiency confers renoprotection by suppressing M1 macrophage activation, inflammatory and profibrotic responses during AKI and its subsequent transition to CKD. Funding: Health and Medical Research Fund (HMRF) of Hong Kong (grant no. 05163596), Research Grants Council of Hong Kong (General Research Fund, grant no. 17118720), and Hong Kong Society of Nephrology-HK Kidney Foundation Research Grant 18.

PUB327

Increased Serum ApoCIII Levels in CKD Patients May Underlie the Impaired Delivery of Cholesterol to Hepatocytes and Increased Cardiovascular Disease (CVD) Risk
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Background: Increased CVD risk underlies the mortality in CKD patients but the underlying mechanisms are not completely defined. We reported earlier that the serum from CKD patients displayed an impaired ability to deliver cholesterol to hepatocytes demonstrating a likely defect in hepatic elimination of cholesterol (as bile acids and biliary cholesterol) returning to the liver from the peripheral tissues via lipoproteins (e.g., VLDL or HDL). Apolipoprotein C-III (ApoCIII) is associated with VLDL and HDL and, not only inhibits lipoprotein lipase and hepatic lipase, but inhibits the uptake of VLDL and HDL by hepatic lipoprotein receptors. Herein we examined the hypothesis that impaired ability of serum from CKD subjects to deliver cholesterol to hepatocytes was associated with increased serum ApoCIII.

Methods: ApoCIII levels were determined by ELISA in serum samples from 32 patients with CKD [stage 3 (N=15) and stage 4/5 (N=17)], 15 patients with established CAD and 15 healthy subjects from our earlier study. One-way ANOVA with Multiple group comparisons was used to determine significance of observed differences.

Results: While ApoCIII levels in healthy subjects and patients with established CAD were not significantly different, significantly higher ApoCIII levels were seen in patients with CKD 3 and CKD 4/5 (See Figure) compared to healthy subjects as well as compared to patients with CAD. This is consistent with the reported decrease in hepatocyte uptake of lipoprotein cholesterol from serum of CKD patients.

Conclusions: Circulating ApoCIII, the catabolism of which is related to kidney function, is increased in CKD and likely impairs the ability of VLDL and HDL uptake by hepatocytes. Using ApoCIII transgenic mice, the mechanism details are currently under investigation.

PUB328

Omega-3 Polysaturated Fatty Acid Attenuates Uremia-Induced Brain Damage in Mice
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Background: Researchers have increasingly demonstrated the relationship between renal impairment and cognitive impairment. Omega-3 polysaturated fatty acid (ω3-PUFA) plays an important role in preserving nerve function. However, neuroprotective effects of ω3-PUFA against uremic condition remain unclear. We are to identify brain damage caused by uremic toxicity and determine the protective effects of ω3-PUFA against uremic toxin.

Methods: We induced uremic condition with renal ischemia reperfusion (IR) injury. 10 weeks male C57BL/6 mice and Fat-1 mice were used for IR injury. 3 days after IR injury, blood, brain and kidney tissue were collected for analysis.

Results: The results showed that K+67 and neuronal nuclei (NeuN) decreased in the brain of uremic mice as compared to wt mice brain, but increased in the ω3-PUFA–treated uremic mice and the brain of uremic Fat -1 mice as compared to the brain of uremic mice. The pro-apoptotic protein expressions were increased, whereas anti-apoptotic protein expression decreased in the brain of uremic mice as compared to wt mouse brain. However, apoptotic protein expression decreased in the ω3-PUFA–treated uremic mice and the brain of uremic Fat -1 mice as compared to the brain of uremic mice. Furthermore, the ω3 PUFA–treated uremic mice and brain of uremic Fat-1 mice protein expression of p-PI3K, p-PDK1, and p-Akt were increased as compared to the brain of uremic mice.

Conclusions: In conclusion, we confirm that uremic toxins damages the brain and causes cell death. ω3 PUFA may play a role in reducing neuronal injuries through PI(3) K-Akt signaling.