Primary aldosteronism, type A intercalated cells and GDF15, a winning trio to control plasma K level

Justine Billiet[1], Luciana Morla[1], Emmanuelle Vidal-Petiot[2], Laurence Amar[3], Lydie Cheval[1], Gilles Crambert[1]

[1] *Université Paris Cité, Sorbonne Université, Inserm, CNRS, Centre de Recherche des Cordeliers, F-75006, Paris*

,

[2] *Service de Physiologie-Explorations Fonctionnelles, AP-HP, Hôpital Bichât, F-75018, Paris*

,

[3] *Unité de recherche et de soin en Hypertension artérielle, AP-HP, Hôpital Européen Georges Pompidou, F-75015, Paris*

Introduction: Primary aldosteronism (PA) affects between 10 and 15% of hypertensive patients Patients present high level of aldosterone, a significant decrease in renin level and hypertension The autonomous and excessive production of aldosterone has a simultaneous effect on the kidneys by stimulating the reabsorption of Na^+ and the secretion of K^+. However, only 30% of patients display hypokalemia, suggesting the development of adaptative processes to counterac the kaliuretic effect of aldosterone.

We previously identified a growth differentiation factor, GDF15 and a membrane protein, the H-K-ATPase type 2 (HKA2) which work together to reduce potassium renal loss by increasing the number of type A intercalated cells (AIC) in cases of dietary potassium deprivation. We hypothesised that this mechanism could exist in PA patients.

Material and methods: In order to investigate GDF15's role in PA, we analysed GDF15 urinar excretion in patients and healthy donors. We then developed a murine model by treating contro (WT) and GDF15 knock-out mice (GDF15KO) with a single intramuscular injection of deoxycorticosterone pivalate (DOCP), an analog of aldosterone. Mice were placed in metabolic cages to measure physiological parameters. Plasma electrolytes were measured by retro-orbital sampling. Muscles were removed to quantify their potassium content. The outer medullary collecting ducts were isolated for cell counting.

Results: Our findings indicate that patients exhibit increased urinary GDF15 levels. Our murine model displays sodium retention, decreased plasma potassium and increased urinary GDF15. In GDF15KO mice, the treatment resulted in a more significant and prolonged hypokalemia. Furthermore, we observed an increase in the number of AIC in WT and found that GDF15KO mice had lower muscle K^+ content.

Conclusion: The findings suggest that kidneys respond to primary aldosteronism by increasing their capacity for potassium retention through a GDF15-dependent pathway.
Topic/s: Physiologie rénale

CT-measured GFR using predominantly early excretory phase CT urography validation against 51Cr-EDTA clearance in living kidney donor candidates

Thomas Stehlé[1], Frédéric Pigneur[2], Emmanuelle Vidal-Petiot[3], Marie-Noëlle Peraldi[4], Eric de Kerviler[5], Martin Flamant[3]

[1] *Service de Néphrologie et Transplantation, APHP - Hôpitaux Universitaires Henri Mondor*
,
[2] *Service d'Imagerie Médicale, APHP - Hôpitaux Universitaires Henri Mondor*
,
[3] *Département de Physiologie-Explorations Fonctionnelles, APHP- Hôpital Bichat*
,
[4] *Service de Néphrologie - Transplantation, APHP - Hôpital Necker*
,
[5] *Service de Radiologie, APHP-Hôpital Saint Louis*

Introduction:

We previously demonstrated that GFR can be measured from 4-phase CT urography using a 7–11-minute excretory phase, validated against iohexol clearance. We aimed to validate CT-measured GFR (CT-mGFR), using predominantly early excretory phase acquisition, with ^{51}Cr-EDTA urinary clearance (EDTA-U) as the reference.

Methods:

We analyzed living kidney donor candidates from a previously published cohort (n=114; 10.1093/ckj/sfad012). CT-mGFR was obtained as previously described. CT segmentations used AI-based methods (SegResNet architecture) with manual correction when required. A chronologically selected calibration subset was used to assess the relationship between excretory phase timing and relative bias versus EDTA-U, enabling timing-based calibration of CT-mGFR values in the remaining patients when required. Agreement with EDTA-U was assessed by median bias (CT-mGFR - EDTA-U), precision (IQR of bias), and accuracy within 10% 15%, 20%, and 30% (P10, P15, P20, P30). We additionally evaluated the performance of hybrid GFR (hGFR), defined as the mean of CT-mGFR and the EKFC equation based on both creatinine and cystatin C, and assessed agreement between 51Cr-EDTA plasma clearance (EDTA-P) and EDTA-U.

Results:

Among the 114 patients from the original cohort, 80 were included in the analysis, with the main reason for exclusion being the absence of an excretory phase acquisition. Median arterial-to-excretory phase delay was 5 min12 s (IQR, 4min44 s – 6min00 s), 10 examinations using the previously described 7–11-minute excretory phase timing. In the calibration subset, (20/70 early excretory phase acquisitions), shorter arterial-to-excretory phase intervals were associated with greater CT-mGFR overestimation. In the 60 analyzed patients, including 50 with excretory phas acquisitions <7 min whose CT-mGFR values were calibrated using the separate calibration subset, median bias of CT-mGFR was −3.0 mL/min/1.73m² (95% CI, −6.9 to -0.2), precision was

15.6 mL/min/1.73m², and P10, P15, P20, and P30 were 60.0% (95%CI, 47.6–72.4), 73.3% (62.1–84.5), 88.3% (80.2–96.5), and 98.3% (95.1–100), respectively. Agreement between hGFR and EDTA-U was higher: median bias 0.3 mL/min/1.73m² (95%CI, −2.4 to 1.0), precision 12.4 mL/min/1.73m², P10, P15, P20, and P30 of 78.3% (95%CI, 67.9–88.8), 93.3% (87.0–99.6), 96.7% (92.1–100), and 100%, respectively; close to agreement between EDTA-P and EDTA-U: median bias −2.3 mL/min/1.73m² (95%CI, −5.0 to −0.7), precision of 8.4 mL/min/1.73m², and P10, P15, P20, and P30 88.3% (95% CI, 80.2–96.5), 93.3% (87.0–99.6), 98.3% (95.1–100), and 100%, respectively.

Conclusion:

In this external cohort of healthy individuals, CT-mGFR showed reliability similar to that observed in previous studies despite shortened excretory phase delays, while hGFR achieved performance close to EDTA-P.

Topic/s: Physiologie rénale

Interplay Between Primary Cilia and Integrin Signaling in Tubular Homeostasis

Rushdi Alghamdi[1, 2], Manal Mazloum[2, 3], Vicky Scata[2], Marielle Cheikh[2], Lydie Cheval[4], Gilles Crambert[4], Fabiola Terzi[2], Frank Bienaimé[2, 3]

[1] *King Abdulaziz University, Jeddah, Saudi Arabia*

,

[2] *Université Paris Cité, INSERM U1151, CNRS UMR8235, Institut Necker-Enfants Malades, Département "Croissance et Signalisation), Paris*

,

[3] *Service d'Explorations Fonctionnelles Rénales Hôpital Necker-Enfants Malades - Paris*

,

[4] *Centre de Recherche des Cordeliers, INSERM, Sorbonne Université, Université Paris Cité, Laboratoire de Physiologie Rénale et Tubulopathies, Paris, France*

Introduction

Chronic kidney disease (CKD) progression is driven by disruption of tubular homeostasis, since tubular epithelial cells actively initiate inflammatory and fibrotic responses following injury. Biomechanical forces, such as fluid flow and extracellular matrix stiffness, are key determinants of CKD and are sensed by apical primary cilia and basolateral integrin-mediated adhesion complexes. Genetic defects affecting cilia, including *PKD1* mutations in autosomal dominant polycystic kidney disease or integrin signaling, lead to CKD. Notably, inactivation of integrin β1 (*Itgb1*) in the developing distal nephron markedly reduces cyst formation in ADPKD mouse models. In addition, a cilium-to-basement membrane signaling axis has recently been identified as a biomechanical driver of cystogenesis, suggesting functional crosstalk between apical and basolateral mechanosensory systems. Here, we investigated the interaction between integrin β1 and primary cilia signaling in regulating tubular responses in the adult kidney.

Materials and Methods

We generated doxycycline-inducible, tubule-specific *Itgb1* knockout mice ($Itgb1^{\Delta tub}$), alone or in combination with *Pkd1* or cilia ablation, to assess their interaction with integrin β1–mediated signaling. Mice were analyzed at 10 weeks of age using quantitative tubular morphometry, fibrosis assessment, immunostaining, qPCR and transcriptomic profiling of microdissected renal tubules.

Results

Deletion of *Itgb1* in adult renal tubules induced a severe fibro-inflammatory phenotype, immune cell infiltration, thickening of the tubular basement membrane, interstitial fibrosis, and marked elongation of the primary cilium. Combined *Itgb1* and *Pkd1* inactivation did not prevent cyst formation but significantly reduced ciliary elongation and attenuated fibro-inflammatory response. Consistently, the upregulation of inflammatory (*Cd3, Ccl2, Ccl5, Cxcl1, Cx3cl1*) and fibrosis markers (*Col1a1, Col4a1, Lamc1, Pdgfb, Tgfb1*) observed in $Itgb1^{\Delta tub}$ kidneys was markedly blunted in $Pkd1^{\Delta tub};Itgb1^{\Delta tub}$ mice. In contrast, combined *Itgb1* and cilia ablation

caused tubular dilation without improving renal fibro-inflammation. These findings indicate that polycystin-1 is required for the deleterious effects of *Itgb1* loss, whereas intact cilia are dispensable.

Conclusion

This study highlights a critical interplay between integrin β1 signaling and primary cilia in maintaining tubular homeostasis and limiting CKD progression. Further studies are needed to elucidate the mechanisms underlying this crosstalk, potentially involving integrin β1–dependent cell–matrix adhesion and mechanosensing of matrix stiffness.

Topic/s: Physiologie rénale

HSP27 promotes activation of parietal epithelial cells and crescent formation in crescentic glomerulonephritis.

Lisa MELIS[1], Hamza Sakhi[2], Khalil El Karoui[1, 2]

[1] *CoRaKiD - Sorbonne Université*

,

[2] *AP-HP- Assistance Publique des Hopitaux de Paris*

Introduction

Crescentic glomerulonephritis (CrGN) is the most severe form of glomerular disease and leads to end stage renal disease in 30-50% of cases. It is characterized by the pathological accumulation of parietal epithelial cells (PEC) forming cellular crescents in the urinary space. Current treatments rely on immunosuppressive therapies and do not directly target molecular pathways driving crescent formation and PEC activation. Heat Shock Protein 27 (HSP27) is a stress-induced chaperone protein with antiapoptotic and pro-proliferative properties. Here, we investigated the role HSP27 in PEC activation and crescent formation.

Material and Methods

To investigate the role of HSP27, we employed both genetic and pharmacological approaches. Mice with PEC-specific deletion of HSP27 (iPEC-Cre :: Hspb1 fl/fl) or treated with the HSP27 inhibitor OGX-427 were subjected to nephrotoxic serum (NTS)–induced CrGN preclinical model Kidney biopsies from patients with CrGN (ANCA associated vasculitis, anti GBM disease, N=13 were analyzed. In vitro, primary PEC cultures were exposed to HB-EGF, with or without HSP27 knockdown or OGX-427 treatment, to assess cell migration, proliferation, and activation markers (including CD44, Claudin-1, CD9, and EGF receptor activation).

Results

HSP27 was strongly overexpressed in PEC within glomerular crescents in both human CrGN biopsies and NTS-treated mice. Moreover, serum HSP27 levels were significantly increased in patients with CrGN. PEC specific deletion of HSP27 delayed disease progression and significantly reduced crescent formation, associated with decreased expression CD44, Claudin-1 and CD9. Importantly, iPEC CRE :: Hspb1 fl/fl mice displayed preserved renal function and reduced albuminuria compared with control mice. We then assessed whether pharmacological inhibition of HSP27 could similarly mitigate crescent formation and PEC activation. Indeed, targeting HSP27 with the pharmacologic inhibitor OGX-427 in mice reduced crescent formation and decreased PEC activation markers expression. In vitro, pharmacologic or genetic silencing of HSP27 in PEC significantly reduced PEC migration and activation (measured by CD44, Claudin-1 expression). Mechanistically, HSP27 knockdown led to decreased EGFR activation, suggesting that HSP27 promotes PEC activation and crescent formation at least partly through the EGFR signaling pathway.

Conclusion

Taken together, our data highlight a role for HSP27 in the development of crescent lesions and pave the way for innovative therapeutic approaches for CrGN patients.
Topic/s: Physiologie rénale