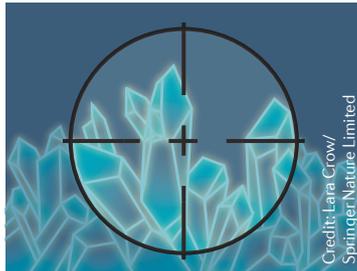


## Calcium phosphate crystals: targets for renoprotection

Hyperphosphatemia is often observed in patients with kidney failure and is associated with poor cardiovascular outcomes. Now, Makoto Kuro-o and colleagues show that even before the onset of kidney failure, the rise in tubular phosphate excretion in response to excess phosphate results in the formation of calcium phosphate (CaP) particles that damage the kidney epithelium.

In response to high dietary phosphate, fibroblast growth factor 23 (FGF23) levels increase and suppress phosphate reabsorption in the kidney. The researchers found that in mice fed a high phosphate diet, high phosphate levels in the tubular fluid led to the formation of CaP crystals. Ex vivo kidney imaging confirmed the presence of these particles in the tubular lumen attached to the brush borders within the cortico-medullary junction; CaP crystals were absent in control mice fed a regular diet or injected with the bisphosphonate aledronate.

CaP crystals induced epithelial damage via Toll-like receptor 4 (TLR4), which was shown to interact with immobilized CaP particles. In mice fed a high phosphate diet, TLR4 accumulated in the apical membrane of tubule cells and, compared with wild-type controls, *Tlr4*<sup>-/-</sup> mice had lower expression of markers of kidney damage, inflammation and fibrosis, despite having similar high levels of urinary phosphate excretion. In cells cultured in vitro, prolonged exposure to CaP particles led to their accumulation within endosomes, disrupted endosomal trafficking and caused cellular damage. However, inhibition of TLR4 signalling in these cells did not completely inhibit inflammation-related signalling and cellular damage. The researchers suggest that, rather than being caused by TLR4 signalling after CaP binding, TLR4–CaP-induced damage is due to TLR4-mediated retention of CaP particles in the lumen, which promotes particle endocytosis and subsequent disruption of endosomal trafficking and damage. Accordingly,



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CaP particles do not accumulate in *Tlr4*<sup>-/-</sup> mice fed a high phosphate diet and *Myd88* deletion, which disrupts TLR4 signalling, is not protective.

The researchers then estimated proximal tubule phosphate excretion levels and nephron numbers in mice; phosphate excretion was also estimated in patients with CKD and correlated with serum FGF23 levels. “Our data indicate that a threshold for phosphate excretion exists, beyond which serum FGF23 increases,” notes Kuro-o. “The subsequent rise in phosphate excretion causes tubule damage and nephron loss via CaP crystals.”

Targeting CaP crystals in the kidney tubular fluid with bisphosphonates in early CKD, before the onset of hyperphosphatemia, might prevent tubule damage and slow CKD progression. “We will test the benefits of dietary phosphate restriction without protein restriction, such as the restriction of phosphate-containing food additives and replacement of animal-based protein with plant-based protein,” explains Kuro-o. “We will also use samples from mice and humans exposed to microgravity conditions to test if bone mineral loss induces kidney tubule damage by increasing the phosphate load excreted per nephron, in which case exercise therapy might be an attractive therapeutic approach.”

Monica Wang

**ORIGINAL ARTICLE** Shiizaki, K. et al. Calcium phosphate microcrystals in the renal tubular fluid accelerate chronic kidney disease progression. *J. Clin. Invest.* <https://doi.org/10.1172/JCI145693> (2021)

## IN BRIEF

### DIABETIC KIDNEY DISEASE

#### Protective circulating proteins in DKD

Progression of diabetic kidney disease (DKD) is variable but little is known about the factors that protect against functional decline in these patients. Using untargeted proteomics profiling, Md Dom and colleagues now report the identification of plasma proteins associated with protection against DKD progression in individuals with type 1 and type 2 diabetes. Elevated levels of three proteins — ANGPT1, FGF20 and TNFSF12 — were associated with nonprogression of DKD. The researchers suggest these proteins could serve as biomarkers to stratify individuals according to their risk of progression.

**ORIGINAL ARTICLE** Md Dom, Z. I. et al. Circulating proteins protect against renal decline and progression to end-stage renal disease in patients with diabetes. *Sci. Transl. Med.* **13**, eabd2699 (2021)

### ACUTE KIDNEY INJURY

#### KIM-1 targeted extracellular vesicles for AKI

Acute kidney injury (AKI) is a common entity for which therapeutics are lacking. Tang et al. now report an approach for the targeted delivery of therapeutics into injured tubule epithelial cells by engineering red blood cell-derived extracellular vesicles that target the injury marker KIM-1 and deliver small interfering RNAs that inhibit *P65* and *Snai1*. Dual suppression of *P65* and *Snai1* using this approach attenuated renal inflammation and fibrosis in mice following ischaemia–reperfusion injury and unilateral ureteral obstruction, and blunted the progression of ischaemic AKI.

**ORIGINAL ARTICLE** Tang, T.-T. et al. Kim-1 targeted extracellular vesicles: a new therapeutic platform for RNAi to treat AKI. *J. Am. Soc. Nephrol.* <https://doi.org/10.1681/ASN.2020111561> (2021)

### COVID-19

#### Kidney involvement in COVID-19

Kidney involvement is common in patients hospitalized with COVID-19; however, the mechanisms remain unclear. A new study of autopsy tissue from kidneys of patients who had died with COVID-19 has identified increased deposition of the complement components C1q, C3, C5b–9 and total immunoglobulin, indicative of complement pathway activation. The researchers also identified high expression levels of Syk, MUC1 and CaMK4, which they propose may also contribute to the development of kidney injury in patients with COVID-19.

**ORIGINAL ARTICLE** Jamaly, S. et al. Complement activation and increased expression of Syk, mucin-1 and CaMK4 in kidneys of patients with COVID-19. *Clin. Immunol.* <https://doi.org/10.1016/j.clim.2021.108795> (2021)

### AMYLOIDOSIS

#### Daratumumab for AL amyloidosis

Systemic immunoglobulin light-chain (AL) amyloidosis is a disease characterized by the deposition of light chain amyloid fibrils produced by clonal CD38<sup>+</sup> plasma cells. In a new phase 3 randomized controlled trial, a significantly higher proportion of patients with newly diagnosed AL amyloidosis who received the anti-CD38 antibody, daratumumab, on top of control therapy achieved the primary end point of a haematologic complete response compared with those who received control treatment only (53.3% versus 18.1%). Patients in the daratumumab group were also more likely than those in the control group to have survival free from major organ deterioration or haematologic progression.

**ORIGINAL ARTICLE** Kastiris, E. et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. *N. Engl. J. Med.* **385**, 46–58 (2021)