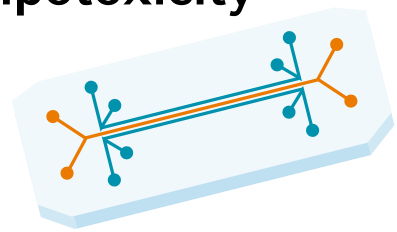
ACUTE KIDNEY INJURY

Blocking glucose to reduce drug-induced lipotoxicity



Credit: Laura Marshall/Springer Nature Limited

Drug-induced nephrotoxicity is a common side effect of chemotherapy and immunosuppressant drugs. Now, using vascularized proximal tubule spheroids-on-a-chip and tissue-embedded metabolic sensors, Yaakov Nahmias and colleagues report that these drugs can lead to increased lipogenesis owing to dysregulated glucose uptake.

The researchers used human proximal tubule cells to develop 3D fluid-filled cysts with apical–basal polarity and showed that even low concentrations (100 nM) of cisplatin or cyclosporin led to upregulation of kidney injury marker 1 and disrupted cell polarization. Then, using a combination of human proximal tubule cells and rat endothelial cells exposed to physiological fluid shear stress, the researchers were able to create 3D vascularized organoids with a gene expression profile that was similar to that of a human proximal tubule. "We embedded these 3D models of the human proximal tubule with oxygen, glucose, lactate and glutamine sensors to measure the metabolic fluxes induced by non-toxic concentrations of cisplatin or cyclosporin," explains Nahmias.

Drug exposure led to a rapid increase in glucose uptake. Given the effect of these drugs on organoid cell polarity, the researchers hypothesize that these nephrotoxic drugs disrupted glucose release from the kidney cell via the basal glucose transporter 2, which they had previously shown to be actively translocated to the basal membrane. "These results suggest that these drugs might disrupt the ability of the kidney to release glucose into the blood, leading to its accumulation," remarks Nahmias. The increase in glucose was followed by a later rise in lipogenesis; the expression of genes associated with lipogenesis (*FASN* and *HMGCR*) was also increased. By contrast, lactate levels were reduced, especially in response to cisplatin (98% reduction). "Whereas fatty acids drive lipid synthesis in mice, human lipogenesis pathways are often glucose-dependent," notes Nahmias. "Increased lipogenesis in kidney cells following glucose accumulation suggests that the microvacuolation observed in drug-induced kidney injury is induced by glucose-driven accumulation of lipid droplets."

The researchers tested this glucose–lipid crosstalk by exposing spheroids to cyclosporin or cisplatin in the presence of empagliflozin, a sodium–glucose cotransporter 2 inhibitor, and showed that blocking glucose uptake had a protective effect. To assess the clinical potential of this combination, they then retrospectively compared parameters of kidney function in 247 patients without kidney disease who had received cyclosporin or cisplatin, with or without concurrent use of empagliflozin. Their analysis showed that serum levels of serum creatinine and uric acid were lower, whereas estimated glomerular filtration rates were higher, in the patients that were being treated with empagliflozin while receiving the nephrotoxic drugs. "These findings suggest that empagliflozin has potential to block the nephrotoxic effect of drugs like cisplatin," comments Nahmias. "We are planning a clinical study to assess this renoprotective effect in patients receiving chemotherapy."

Monica Wang

ORIGINAL ARTICLE Cohen, A. et al. Mechanism and reversal of drug-induced nephrotoxicity on a chip. *Sci. Transl. Med.* **13**, eabd6299 (2021)

IN BRIEF

FIBROSIS

A SOX-9–NAV3–YAP1 axis in kidney fibrosis

Fibrosis is a common end point in various forms of chronic kidney disease; however, the mechanisms underlying kidney fibrosis are not fully understood. New findings identify a role for a SOX9–NAV3–YAP1 axis in the progression of kidney fibrosis. Raza et al. show that the transcription factor SOX9 is required for experimentally induced kidney fibrosis in mice, which is associated with increased abundance and colocalization of the cytoskeleton-associated factor NAV3. In vitro, NAV3 was required for the transdifferentiation of mouse kidney pericytes into myofibroblasts and activation of pro-fibrotic YAP1.

ORIGINAL ARTICLE Raza, S. et al. SOX9 is required for kidney fibrosis and activates NAV3 to drive renal myofibroblast function. *Sci. Signal.* **14**, eabb4282 (2021)

ARTERIOVENOUS FISTULAE

A nanoparticle approach to prevent AVF failure

Failure of arteriovenous fistulae (AVF) can occur as a result of venous neointimal hyperplasia (VNH) leading to venous stenosis. In new research, Singh et al. show that inhibition of *Ier-3* — an immediate early response gene that is associated with VNH and stenosis in mouse models of AVF — using $1\alpha,25(OH)_2D_3$-encapsulated nanoparticles, reduced VNH and stenosis formation in a porcine AVF model. Release of $1\alpha,25(OH)_2D_3$ into the perivascular AVF space from poly(lactic-co-glycolic acid) nanoparticles embedded in a pluronic F127 hydrogel improved AVF flow and haemodynamics, and reduced inflammation, apoptosis and fibrosis.

ORIGINAL ARTICLE Singh, A. K. et al. 1α,25-Dihydroxyvitamin D3 encapsulated in nanoparticles prevents venous neointimal hyperplasia and stenosis in porcine arteriovenous fistulas. *J. Am. Soc. Nephrol.* https://doi.org/10.1681/ASN.2020060832 (2021)

PROTEIN DEGRADATION

ER-associated degradation of nephrin

Endoplasmic-reticulum-associated protein degradation (ERAD) targets misfolded proteins in the endoplasmic reticulum (ER) for proteasome-mediated degradation. Now, Yoshida et al. show that the SEL1L–HRD1 ERAD complex has a key role in slit diaphragm formation and glomerular filtration function. They demonstrate that nephrin is an endogenous ERAD substrate and that ERAD mediates the degradation of nephrin mutants. ERAD deficiency prevented nephrin maturation, leading to its retention in the ER. Moreover, podocyte-specific *Sel1L*-knockout mice show slit diaphragm impairment and severe congenital nephrotic syndrome.

ORIGINAL ARTICLE Yoshida, S. et al. Endoplasmic reticulum-associated degradation is required for nephrin maturation and kidney glomerular filtration function. *J. Clin. Invest.* https://doi.org/10.1172/JCI143988 (2021)

COVID-19

Soluble ACE2 in SARS-CoV-2 infection

SARS-CoV-2 gains entry to host cells via angiotensin-converting enzyme 2 (ACE2). Now, research demonstrates a role for a soluble form of ACE2 (sACE2) and vasopressin in mediating SARS-CoV-2 entry into susceptible cells. Using kidney HK-2 cells, which are highly susceptible to SARS-CoV-2 infection, Yeung et al. show that interaction of the SARS-CoV-2 spike protein with sACE2 or with a complex of sACE2 plus vasopressin mediates receptor-mediated endocytosis of the virus via type 1 angiotensin and vasopressin V1b receptors, respectively.

ORIGINAL ARTICLE Yeung, M. L. et al. Soluble ACE2-mediated cell entry of SARS-CoV-2 via interaction with proteins related to the renin–angiotensin system. *Cell* https://doi.org/10.1016/j.cell.2021.02.053 (2021)