GLOMERULAR DISEASE

A link between mitochondrial dysfunction and innate immune activation in FSGS

Mutations in mitochondrial DNA (mtDNA) and mitochondrial dysfunction have been implicated in the pathogenesis of focal segmental glomerulosclerosis (FSGS). Now, Jeremy Duffield and colleagues report that in mice, a loss-of-function mutation in the *Cox10* gene, which encodes a cofactor for complex IV of the electron transport chain, results in activation of the innate immune system and the development of FSGS.

"Mitochondria are a vestige of a symbiosis between eukaryotic cells and prokaryotic cells, so the mitochondria are hiding in plain sight from the intracellular innate immune sensing system," explains Duffield. "We were interested in investigating whether dysfunctional mitochondria can activate the intracellular immune response."

To answer this question, the researchers generated mice with nephron-specific knockout of *Cox10*. They report that these mice develop a severe, early-onset form of FSGS with tubulointerstitial damage, fibrosis, inflammation and premature death due to kidney failure.

"We found evidence that not only does *Cox10* silencing result in partial loss of mitochondrial function, but also that it results in activation of the intracellular sensing system for foreign or viral DNA," says Duffield. Additional experiments suggested that loss of *Cox10* in kidney epithelial cells leads to leakage of mtDNA into the cytosol and activation of the DNA sensor STING, resulting in the induction of an interferon response and activation of the innate immune system.

The researchers conclude that loss of COX10 is sufficient to cause severe FSGS. In addition, they hypothesize that the release of mtDNA may be a novel mechanism that contributes to the pathogenesis of FSGS in the setting of mitochondrial dysfunction.

Ellen F. Carney

ORIGINAL ARTICLE Baek, J.-H. et al. Deletion of the mitochondrial complex-IV co-factor heme A:farnesyl-transferase causes focal segmental glomerulosclerosis and interferon response. *Am. J. Pathol.* https://doi.org/10.1016/j.ajpath.2018.08.018 (2018)

RENAL TRANSPLANTATION

3D printing aids transplantation planning

Kidney transplantation poses particular surgical challenges when the organ recipients are young children. Now, Chandak and colleagues show that 3D printing can be used to determine operative feasibility in cases of complex paediatric renal transplantation.

The researchers report three cases of young children with end-stage renal disease that required transplantation, each posing distinct challenges to the surgical team. In the first case, there was a large size difference between the young child's small abdomen and the adult donor kidney. The second patient presented with vascular anatomy abnormalities and the third child required a staged operation due to severe aneurysmal disease.

Chandak says that in all three cases the viability of transplantation was difficult to ascertain based on the review of conventional imaging. "These circumstances would normally require on-table exploration of the child to confirm operative feasibility and we were keen to use patient-specific 3D printing to pre-operatively assess feasibility and reduce risk," he explains.

Using anatomical geometry data obtained from MRI or computed tomography (CT) scans, the researchers created patient-specific models of relevant anatomical structures. The models included not only donor and recipient kidneys but also vasculature and the abdominal cavity. Following image segmentation and editing, the models were verified by a radiologist and printed using polyjet technology. The final 3D-printed models were then used in multidisciplinary discussions ahead of transplantation to enable simulation and detailed planning of the surgical procedure.

"In our centre, 3D printing is now an integral part of the clinical workf low, and patient-specific 3D models are used in our multidisciplinary discussions of complex cases," remarks Chandak. "We hope that accessing this technology will provide clinical teams with an additional layer of planning opportunity when dealing with high-risk transplantation in children."

Monica Wang

ORIGINAL ARTICLE Chandak, P. et al. Patient-specific 3D printing: a novel technique for complex pediatric renal transplantation. *Ann. Surg.* https://doi.org/10.1097/SLA.0000000000003016 (2018)

POLYCYSTIC KIDNEY DISEASE

Arginine auxotrophy in PKD

In renal cell carcinoma (RCC), decreased expression of arginosuccinate synthase (ASS1) results in arginine auxotrophy; therefore, arginine deprivation has been proposed as a potential therapy. Now, Robert Weiss and colleagues report that arginine auxotrophy is also a feature of autosomal dominant polycystic kidney disease (ADPKD).

The researchers found that ASS1 is predominantly expressed in the proximal tubules in healthy human kidneys. In patients with ADPKD, ASS1 expression is maintained in non-atrophic proximal tubules but is reduced or absent in atrophic tubules. In RCC, *ASS1* expression is reduced owing to promoter methylation; however, the *ASS1* promoter was not methylated in the ADPKD samples. The researchers suggest that reduced ASS1 expression in ADPKD is the result of loss of proximal tubule cells owing to tissue atrophy.

Under conditions of arginine depletion, the proliferation and viability of *Pkd1*$^{-/-}$ cell lines was reduced compared to wild-type cells. In addition, using in vitro and ex vivo cyst assays, the researchers showed that lowering the concentration of arginine in the culture media reduces cystogenesis in a dose-dependent manner. "Glucose and glutamine reprogramming have previously been described in PKD, but our study is the first to describe arginine reprogramming," notes Weiss.

Metabolomics analyses showed that arginine depletion mostly affected the glutamine and proline pathways and led to increased glutamine levels in wild type and *Pkd1*$^{-/-}$ cell lines. Moreover, when arginine deiminase (ADI) was used to deplete arginine in cell cultures, *Pkd1*$^{-/-}$ cells produced more glutamate than did wild-type cells. Based on these findings, the researchers suggest that arginine deficiency could lead to glutamine addiction in PKD.

"Decreasing circulating arginine levels is likely to affect cyst production but not normal tissues, as the latter can produce their own arginine," says Weiss. "We foresee a trial of dietary arginine depletion and possibly ADI therapy in patients with ADPKD."

Monica Wang

ORIGINAL ARTICLE Trott, J. F. et al. Arginine reprogramming in ADPKD results in arginine-dependent cystogenesis. *Am. J. Physiol. Renal Physiol.* https://doi.org/10.1152/ajprenal.00025.2018 (2018)