POLYCYSTIC KIDNEY DISEASE

Crystal deposition aids cystogenesis

Variability in the rate of disease progression among patients with autosomal dominant polycystic kidney disease (PKD) suggests an environmental component in disease pathogenesis. New findings show that deposition of calcium oxalate (CaOx) crystals activates PKD-associated signalling pathways to flush out lodged crystals but also triggers cyst formation in PKD. "Our first major finding is the discovery of a fundamental, renoprotective mechanism whereby renal tubules dilate deliberately in response to lodged micro-crystals in an effort to flush them out," says Thomas Weimbs. "The second is that the same renoprotective mechanism inadvertently triggers cyst growth in PKD and accelerates progression of the disease."

Weimbs explains that the basis for this study was prior work that culminated in the 'third-hit model', which posits that a form of kidney injury is needed, in addition to the gene mutation, to generate cysts in PKD. "I thought that there must be a common form of insult that human kidneys experience on a regular basis in order for the third-hit model to make sense. Furthermore, if this form of insult was under the influence of external factors, such as dietary intake of 'something', it could possibly explain the high variability of disease progression in PKD," says Weimbs. "I realised that micro-crystals fit these criteria."

The researchers show that CaOx crystal deposition induces activation of mTOR and STAT3 signalling pathways along with tubule dilation and hypertrophy. Blocking mTOR signalling attenuated the cellular response and led to an accumulation of CaOx crystals in tubules, suggesting that tubule dilation is a mechanism to clear lodged crystals. Deposition of CaOx or calcium phosphate crystals exacerbated cystogenesis and accelerated disease progression in rat models of PKD. Moreover, in patients with PKD, urinary levels of citrate, an inhibitor of calcium crystal formation, were inversely correlated with disease severity. "In PKD, tubule dilation is the first step towards cyst formation and this step is exacerbated by micro-crystals" explains Weimbs. "Therefore, any increase in 'crystal burden', such as through dietary means, could worsen PKD progression in patients. The good news is that we can try to do something about that by reducing the renal crystal burden."

Susan J. Allison

ORIGINAL ARTICLE Torres, J. A. et al. Crystal deposition triggers tubule dilation that accelerates cystogenesis in polycystic kidney disease. *J. Clin. Invest.* https://doi.org/10.1172/JCI128503 (2019)

DIABETIC KIDNEY DISEASE

A novel approach to targeting TGFβ1

Transforming growth factor-β1 (TGFβ1) has a key role in the development of diabetic nephropathy (DN). However, existing approaches to target TGFβ1 have failed to improve outcomes in clinical trials. Now, Gao et al. suggest that targeting the transcriptional repressor protein YY1 could be a promising therapeutic strategy for DN.

Using a mass spectrometry-based DNA–protein interaction screen in human renal mesangial cells (HRMCs), the researchers identified YY1 as a potential transcriptional regulator of TGFβ1. They found that YY1 was upregulated in high-glucose treated but not in low-glucose treated HRMCs.

Further analyses confirmed that YY1 binds directly to the promoter region of the *TGFB1* gene and represses its transcription. Consistent with this finding, overexpression of YY1 reduced the expression of TGFβ1 and downstream proteins in HRMCs, whereas knockout of YY1 had the opposite effect.

In mouse models of DN, expression of YY1 negatively correlated with TGFβ1 expression and the severity of renal fibrosis. Moreover, knockdown of YY1 in glomeruli led to increased expression of TGFβ1 and exacerbated renal fibrosis, whereas overexpression of YY1 suppressed TGFβ1 expression and attenuated the development of DN in mice.

Renal biopsy samples from patients with mild DN had significantly higher glomerular expression of YY1, lower expression of TGFβ1 and less severe glomerulosclerosis than those from patients with severe DN. As the patients had similar diabetes durations, Gao et al. suggest "YY1 may play a renoprotective role by downregulating TGFβ1 in the setting of diabetic pathology".

Finally, the researchers show that a small molecule, eudesmin, upregulated YY1 in HRMCs and attenuated renal fibrosis by upregulating YY1 in DN mice. They conclude that YY1 is a critical transcriptional suppressor of TGFβ1 and suggest that targeting YY1 using small molecules is a potential novel therapeutic approach for DN.

Ellen Carney

ORIGINAL ARTICLE Gao, P. et al. Yin Yang 1 protein ameliorates diabetic nephropathy pathology through transcriptional repression of TGFβ1. *Sci. Transl Med.* **11**, eaaw2050 (2019)

CHRONIC KIDNEY DISEASE

APOL1 risk variants induce opening of the mitochondrial permeability transition pore

A recent study by David Friedman and colleagues provides new insight into the mechanisms by which apolipoprotein L1 (APOL1) risk variants injure kidney cells. "These variants were identified almost 10 years ago, but we still don't have a good understanding of how they increase the risk of kidney disease," says Friedman. "There is also surprisingly little consensus on how the behaviour of the risk variants differs from that of the non-risk variants with respect to trafficking patterns or binding partners."

To investigate the molecular behaviour of APOL1, the researchers used inducible cell lines that stably expressed either the risk or non-risk variants. They report that all of these variants translocate into mitochondria via the same import pathway and that blocking this pathway abrogates APOL1 risk variant-mediated cell death.

The researchers also show that once inside the mitochondria, the risk variants oligomerize to form multimers, whereas the non-risk variant remains monomeric. Both the risk and non-risk variants bind to components of the mitochondrial permeability transition pore, but only the risk variants activate pore opening, which leads to cell death.

"When comparing the risk and non-risk variants, the trafficking patterns and binding partners are similar, but the actions at the pore are different," summarizes Friedman. "The difference in how the pore responds to APOL1 risk and non-risk variants may help to explain how the risk variants cause kidney disease." The researchers now plan to investigate the effects of APOL1 variants in vivo. "Just as the risk variants are associated with different types of kidney disease, they may cause disease by different mechanisms, so we don't think that opening of the pore is necessarily the only mechanism at work in APOL1 kidney disease," says Friedman.

Ellen F. Carney

ORIGINAL ARTICLE Shah, S. S. et al. APOL1 kidney risk variants induce cell death via mitochondrial translocation and opening of the mitochondrial permeability transition pore. *J. Am. Soc. Nephrol.* https://doi.org/10.1681/ASN.2019020114 (2019)