GENETICS

# Toxicity of APOL1 channel activity

The G1 and G2 variants of APOL1 are associated with an increased risk of kidney disease; however, the mechanism by which these risk variants cause kidney injury is unclear. New findings show that, unlike the G0 reference allele, the G1 and G2 variants form cytotoxic cation channels at the surface of cells, which triggers an influx of $Na^+$ and $Ca^+$ across the plasma membrane and leads to cell death. "The discovery that cation influx has an important role in APOL1-associated cytotoxicity can help us elucidate the downstream pathways by which G1 and G2 induce cell death," explains Joseph Giovinazzo. "For example, $Ca^+$ has been linked to activation of a multitude of signalling and cell death pathways, cytoskeletal rearrangements and podocyte foot process effacement, and it is possible that any of these processes are induced downstream of $Ca^+$ influx."

Using confocal immunofluorescence microscopy, the researchers show that following release from the endoplasmic reticulum, all three variants traffic to the plasma membrane. At the plasma membrane, use of live-cell microscopy with $Ca^+$ sensors and APOL1 impermeable cations showed that cytoplasmic influx of $Ca^+$ and $Na^+$ precedes the swelling and lysis of cells that express the G1 and G2, but not the G0 variant. The researchers propose that a regulatory mechanism exists that prevents G0 cytotoxicity. Artificial acidification of the non-toxic G0 variant after plasma membrane localization activated the channel and induced cell death. "Our work suggests that the APOL1 risk variants may be more pH sensitive and therefore form channels more readily than non-risk variants," says Giovinazzo. "Our live-cell microscopy and time course experiments have also allowed us to build a timeline of events through which the risk variants lead to cell death. Perhaps most importantly, the channel activity of the risk variants at the plasma membrane could make these variants amenable to therapeutic targeting. We anticipate that future efforts will be directed towards understanding the channel structure and the development of compounds to block APOL1 channel activity."

*Susan J. Allison*

**ORIGINAL ARTICLE** Giovinazzo, J. A. et al. Apolipoprotein L-1 renal risk variants form active channels at the plasma membrane driving cytotoxicity. *eLife* **9**, e51185 (2020)

ACUTE KIDNEY INJURY

# Renoprotection through PXR–AKR1B7

The metabolic regulator pregnane X receptor (PXR; encoded by *Nr1i2*) is dysregulated in several diseases, including chronic kidney disease (CKD), and is the focus of a new acute kidney injury (AKI) study by Yue Zhang, Zhanjun Jia, Aihua Zhang and colleagues. "Metabolic defects in kidney tubular cells contribute to the pathogenesis of AKI and we wanted to examine the role of PXR in this process," explains Yue Zhang.

PXR was reduced in kidney biopsy samples of patients with AKI compared with healthy kidneys, and the intensity of PXR staining correlated negatively with blood urea nitrogen (BUN) and serum creatinine (sCr) levels. PXR expression also decreased in a time-dependent manner in the kidneys of mice with cisplatin-induced AKI.

In rats exposed to cisplatin, loss of PXR (*Nr1i2*$^{-/-}$) aggravated tubular injury and significantly increased levels of BUN and sCr compared with wild-type controls; swollen mitochondria and disrupted cristae were also more abundant in the kidneys of *Nr1i2*$^{-/-}$ rats. These effects were accompanied by reduced expression of mitophagy-related genes and defective mitochondrial fatty acid oxidation. Inhibiting mitochondrial stress improved cisplatin-induced AKI in both wild-type and *Nr1i2*$^{-/-}$ rats. Kidney proteomics showed that PXR deletion significantly reduced the expression of aldo-keto reductase family 1 member B7 (AKR1B7), which was validated as a transcriptional target of PXR.

In contrast to PXR loss, administration of the PXR agonist pregnenolone-16α-carbonitrile (PCN) was renoprotective in murine models of cisplatin-induced AKI, but only in animals with intact PXR. In wild-type mice, in vivo overexpression of PXR or AKR1B7 induced by plasmid injection also protected animals against cisplatin-induced AKI and restored mitochondrial function.

"We are working on the generation of new PXR agonists, which might have therapeutic potential in AKI," remarks Jia. "We also plan to study the potential role of PXR in the pathogenesis of CKD and in AKI to CKD transition," adds Aihua Zhang.

*Monica Wang*

**ORIGINAL ARTICLE** Yu, X. et al. Nuclear receptor PXR targets AKR1B7 to protect mitochondrial metabolism and renal function in AKI. *Sci. Transl. Med.* **12**, eaay7591 (2020)

GLOMERULAR DISEASE

# Role of infection and molecular mimicry in the pathogenesis of anti-GBM disease

Anti-glomerular basement membrane (GBM) disease is associated with *HLADRB1*1501* and characterized by circulating autoantibodies against the GBM. A recent study by Zhao Cui and colleagues reports that a microbial peptide can activate autoreactive T and B cells and contribute to the pathogenesis of this disease.

"Infections can initiate most forms of glomerulonephritis but the specific pathogens and pathways that lead to auto-immunity and inflammatory activation are unclear," says Cui. "Anti-GBM disease is the classical model of autoimmune glomerulonephritis, and the autoantigen and critical amino acids have been identified. We used bioinformatics tools to search for pathogen peptides that may mimic the critical amino acids of the autoantigen and activate autoreactive lymphocytes. This method helped us to narrow down the candidate microbial peptides from thousands to 36, which made the subsequent laboratory experiments feasible."

The researchers identified antibodies against nine of the candidate microbial peptides in serum samples from patients with anti-GBM disease. Immunization with one of these nine peptides, B7 derived from *Actinomyces* species, induced proteinuria, linear IgG deposition on the GBM and crescent formation in Wistar Kyoto rats and in humanized *HLADR15* transgenic mice via cross-reactivity of lymphocytes.

"Our findings implicate a role for infection and molecular mimicry in the pathogenesis of anti-GBM disease," concludes Cui. "Similar mechanisms might also be found in other autoimmune forms of glomerulonephritis. However, molecular mimicry is just one of many pathways between infections and glomerulonephritis and further investigations are needed to define these pathways and develop preventive approaches."

*Ellen F. Carney*

**ORIGINAL ARTICLE** Gu, Q. et al. Experimental antiglomerular basement membrane GN induced by a peptide from *Actinomyces*. *J. Am. Soc. Nephrol.* **31**, 1282–1295 (2020)