VIRAL NEPHROPATHY

Newly identified parvovirus causes kidney failure in mice

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Mouse models of chronic kidney disease (CKD) often depend on acute, short-term injuries. Now, Ben Roediger, Wolfgang Weninger and colleagues describe a new virus that infects the mouse kidney and enables "a comprehensive clinicopathological workup of CKD in a natural small animal model".

"We noticed that certain mice in our animal facility were succumbing prematurely to a 'mystery' kidney disease," explains Roediger. "The disease primarily affected immunodeficient mice so we suspected an underlying infectious cause." Using a metagenomics approach the researchers identified a novel, highly divergent and highly infectious mouse parvovirus, which they named mouse kidney parvovirus (MKPV), as the cause of renal failure in these animals. Parvovirus infections are usually asymptomatic but MKPV has a marked tropism for renal tubular epithelial cells and causes progressive damage over several months, leading to renal failure and death.

The researchers detected viral DNA by PCR in the serum, urine and faeces of infected mice. In addition, using in situ hybridization, they identified MKPV sequences in kidney tubular cells with intranuclear inclusion bodies. Viraemia preceded renal disease and positively correlated with its severity. Importantly, in the early asymptomatic stages of the disease when there was no viraemia, MKPV was only detectable in the kidney.

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MKPV causes inclusion body nephropathy (IBN), which is associated with fibrotic changes in the kidney. Consistent with this finding, RNA sequencing revealed that renal injury markers (*Havcr1* and *Lcn2*), transforming growth factor-β, collagen and fibrinogen-associated genes, all of which are linked to fibrosis, were upregulated in the kidneys of infected mice.

Further analysis of gene and protein expression in IBN kidneys indicated that an increase in macrophages, myofibroblast development and loss of epithelial cells are key events in MKPV-driven kidney pathology. MKPV infection increased the frequency of renal macrophages that expressed the activation markers CD86 and CD206; increased expression of complement genes provided additional evidence of local immune activation. A myofibroblast-like cell population ($CD45^{-}FAP^{+}CD24^{hi}$) was also enriched and the expression of the *Acta2* and *Vim* myofibroblast markers was increased in infected kidneys. By contrast, proteins expressed by tubular epithelial cells, such as solute carrier proteins, were downregulated and the frequency of $EpCAM^{hi}CD29^{+}$ epithelial cells was reduced, implying epithelial cell loss.

To assess the potential of MKPV infection as a renal fibrosis model, the investigators compared it to the commonly used unilateral ureteral obstruction model. In both models, many genes that drive kidney fibrosis were overexpressed but, interestingly, in MKPV-infected kidneys two additional genes, *Clec9a* and *Itgae*, were upregulated. These genes are expressed by a subset of dendritic cells (cDC1) that was expanded in infected mice and is thought to be associated with CKD in humans. Another similarity between the MKPV infection model and patients with CKD is a characteristic decrease in the levels of urinary epidermal growth factor, which is a biomarker of human kidney fibrosis.

Kidney disease following MKPV infection was mainly observed in mice with severe immune deficiency (lacking T cells, B cells and natural killer cells) whereas immunocompetent and athymic (T cell-deficient) nude mice, were only mildly affected, suggesting that host immunity can limit the viral infection and prevent kidney pathology. "Importantly, MKPV-induced nephropathy shares many clinicopathological similarities with polyomavirus-associated nephropathy, which has emerged as a significant cause of morbidity in kidney transplant recipients," remarks Weninger. "We have defined a natural infection system in which to study fibrotic responses to viral infection in the kidney."

"We now plan to further investigate the kinetics of MKPV infection in immune-competent and immune-deficient mice," explains Weninger. "We are presently trying to identify the MKPV entry receptor on renal tubular cells and in future we may be able to use the viral backbone for gene targeting of tubular epithelial cells," adds Roediger.

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