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BASIC RESEARCH

Critical role of mTORC1 in tubular cells

New data suggest that mammalian target of rapamycin complex 1 (mTORC1) has important roles in renal tubular homeostasis, mitochondrial metabolism and the ischaemic stress response. "As several experimental therapies using mTOR inhibitors target the kidney—and use of these agents in transplantation and cancer therapy is increasing—we believe it is essential to understand the organ-specific functional role of this important kinase," explain authors Florian Grahammer and Tobias B. Huber.

The researchers report that mice with tubule-specific deletion of mTORC1 showed increased urine production and other evidence of a defect in urine-concentrating mechanisms, as well as increased renal fibrosis, reduced numbers of mitochondria and abnormal mitochondrial morphology compared to wild-type controls. Consistent with these findings, gene sets linked to mitochondrial metabolism, mitochondrial biogenesis and transcellular transport processes involved in urine concentration were downregulated, and those related to cell division, DNA repair, the cell cycle, transcription and the extracellular matrix were upregulated in the transgenic mice. The researchers also found that the severity of tubular damage after ischaemia–reperfusion injury was increased in mTORC1-deficient mice compared with wild-type littermates.

"Deletion of mTORC1 in renal tubules leads to dysfunction and loss of mitochondria, which in turn leads to a loss of transport capacity and finally loss of urinary concentrating ability," concludes Huber. He suggests that delayed graft function in renal transplant recipients who receive early treatment with mTORC1 inhibitors might be the result of increased tubular cell apoptosis and reduced tubular cell proliferation after ischaemic injury.

Ellen F. Carney

Original article Grahammer, F. *et al*. mTORC1 maintains renal tubular homeostasis and is essential in response to ischemic stress. *Proc. Natl Acad. Sci*. doi:10.1073/pnas.1402352111