Nature Reviews Nephrology | Published online 15 May 2015; doi:10.1038/nrneph.2017.70

DIABETIC NEPHROPATHY

Glucose metabolic flux in DN

> PKM2 ... also improves mitochondrial dysfunction

Diabetic nephropathy (DN) is a common cause of end-stage renal disease and is thought to be caused, at least in part, by hyperglycaemia-induced mitochondrial dysfunction. New research shows that activation of pyruvate kinase M2 (PKM2) can protect podocytes from glucose-induced damage by increasing glucose metabolic flux and mitochondrial metabolism. "This finding was surprising, as previously the belief was that activation of glycolysis or aldose reductase pathways by glucose damages podocytes," explains researcher George King. "Our findings also identify that activation of PKM2, a key glycolytic enzyme, increases glycolytic flux, but unexpectedly also improves mitochondrial dysfunction induced by diabetes."

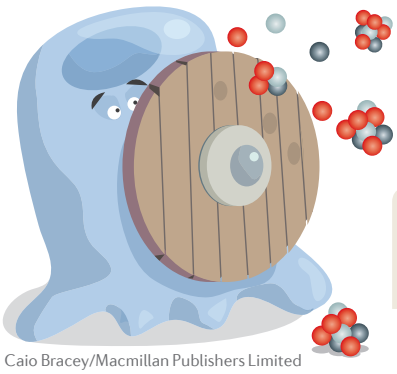
To assess mechanisms by which cells are protected from the adverse effects of hyperglycaemia, King and colleagues performed proteomic and metabolomic analyses on glomeruli isolated from individuals with extreme duration of diabetes with and without histologic evidence of DN. "Our study was initiated based on the clinical findings of the Joslin Medallist Study, which characterized a cohort of 1,000 individuals who had been living with type 1 diabetes mellitus for over 50 years," says King. "We reported that a considerable proportion of these individuals do not have severe kidney or eye diseases, suggesting that some endogenous factors might protect them from the toxic effects of hyperglycaemia." Surprisingly, the analyses revealed higher levels of proteins related to glucose metabolism and mitochondrial function in glomeruli from individuals who were protected from DN than in individuals with renal disease, including pathways that had previously been linked to the vascular complications of diabetes. Subsequent metabolomics analysis showed a reduction in glucose metabolites from the glycolytic, sorbitol and methylglyoxal detoxification pathways in protected kidneys, suggesting that cells from these individuals have an increased ability to process these potentially harmful metabolites.

The researchers chose to further investigate the role of PKM2, which was upregulated in glomeruli from protected individuals and correlated with estimated glomerular filtration rate. In contrast to levels in protected glomeruli, podocytes exposed to high glucose levels and glomeruli from diabetic mice had reduced pyruvate kinase activity and lower levels of PKM2 activity. In line with these findings, diabetic mice with podocyte-specific deletion of *Pkm2* developed more severe renal disease than wild-type diabetic mice.

The researchers then assessed the effects of the small PKM2 activator, TEPP-46. In mouse podocytes, TEPP-46 inhibited glucose-mediated increases in sorbitol and diacylglycerol by increasing glycolytic flux and increasing indices of mitochondrial metabolism. In mice with established diabetes, TEPP-46 led to an increase in pyruvate kinase activity, lower levels of sorbitol, methylglyoxal and diacylglycerol, and induced the expression of *Opa1*, indicative of mitochondrial fusion. TEPP-46 also reversed reduced albuminuria and reversed diabetes-induced kidney pathology in wild-type mice, but not in *Pkm2*-knockout mice.

King says that future work will document whether these glomerular changes also occur in people with diabetes mellitus of shorter duration. "We are working with companies to develop PKM2 activators that can be tested in clinical trials of patients with DN," he adds.

Susan J. Allison



Caio Bracey/Macmillan Publishers Limited

ORIGINAL ARTICLE Qi, W, *et al.* Pyruvate kinase M2 activation may protect against the progression of diabetic glomerular pathology and mitochondrial dysfunction. *Nat. Med.* http://dx.doi.org/10.1038/nm.4328