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OBESITY

Shielding mitochondria from lipotoxicity prevents renal injury

> SS-31 … abolished cell death and glomerular and tubular injury, and restored renal AMP kinase signalling

Lipid accumulation in obesity leads to severe renal damage through unknown mechanisms. Now, Hazel Szeto and colleagues show that in mice, a high-fat diet (HFD) alters mitochondrial structure and function, resulting in glomerulopathy and tubular injury. These effects can be prevented by treatment with the mitoprotective peptide SS-31, which targets cardiolipin.

The researchers report that 28 weeks of a HFD resulted in a reduction in mitochondrial size, loss of cristae membranes, and decreased matrix density in podocytes, glomerular endothelial cells and proximal tubular cells. The mitochondrial injury led to accumulation of lipid droplets, endoplasmic reticulum stress, autophagy, and/or apoptosis, eventually resulting in proteinuria, inflammation, and fibrosis. "For the first time, we showed that a HFD causes endothelial cell injury and loss of glomerular capillaries, resulting in persistent upregulation of vascular endothelial growth factor and glomerular inflammation," adds Szeto.

Treatment with SS-31 prevented HFD-induced lipid accumulation and mitochondrial damage in all renal cell types, abolished cell death and glomerular and tubular injury, and restored renal AMP kinase signalling, but had no effect on weight gain, insulin resistance or hyperglycaemia.

"As SS-31 has no effect on blood glucose, body weight or blood pressure, it can be used in combination with standard of care," says Szeto. "SS-31 was well-tolerated in several phase I and II clinical trials, so we can readily move to a proof-of-concept clinical trial for chronic kidney disease associated with metabolic syndrome. In addition, the NIH has expressed interest in a phase II trial for diabetic nephropathy."

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ORIGINAL ARTICLE Szeto, H. H. *et al.* Protection of mitochondria prevents high fat diet-induced glomerulopathy and proximal tubular injury. *Kidney Int.* http://dx.doi.org/10.1016/j.kint.2016.06.013 (2016)