RENAL INJURY

**KLF6 PROTECTS
INJURED PODOCYTES**

A new study suggests that *Krüppel-like factor 6* (*KLF6*) is an early inducible response gene that maintains mitochondrial function and prevents apoptosis of injured podocytes through the transcriptional regulation of cytochrome c oxidase assembly protein (*SCO2*). Mitochondrial dysfunction has previously been implicated in glomerular diseases and various KLFs have known roles in mitochondrial regulation.

Mallipattu *et al.* observed that *KLF6* expression was significantly reduced in HIV-1-infected human podocytes and in renal biopsy specimens from patients with HIV-associated nephropathy or focal segmental glomerulosclerosis (FSGS), compared with uninfected podocytes and normal renal tissue. These data suggest that loss of *KLF6* might have a role in podocyte injury.

To investigate whether *Klf6* contributes to mitochondrial maintenance, the researchers knocked-down *Klf6* in the podocytes of C57Bl/6 mice. Phenotypic analysis showed a 3.5-fold increase in albuminuria in these mice compared with controls, but no glomerulosclerosis. Administration of adriamycin (ADR), which causes nephropathy in C57Bl/6 mice that harbour mutations in mitochondrial genes but not in those with normal mitochondrial function, induced FSGS in the *Klf6*-knockout mice. Ultrastructural examination of podocytes from these mice revealed dysmorphic mitochondria as well as decreased mitochondrial membrane potential, oxygen consumption rate and ATP levels. In cultured human podocytes *Klf6* levels significantly increased within 6 h of ADR exposure, indicating fast induction of protein expression in response to injury.

Finally, *in vitro* studies implicated *SCO2*—a mitochondrial membrane-bound metallochaperone—as a major downstream target of *KLF6* that mediates protection against podocyte injury. Knockdown of *SCO2* in human podocytes resulted in increased levels of cleaved caspase-9 and release of cytochrome c, indicating activation of the intrinsic apoptotic pathway.

The researchers conclude that *KLF6* is an essential transcriptional regulator of mitochondrial function and podocyte apoptosis. They now plan to investigate whether other genes act in concert with *KLF6* and *SCO2* to protect podocytes from injury.

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