Nature Reviews Nephrology **11**, 197 (2015); published online 10 February 2015; doi:10.1038/nrneph.2015.13

ACUTE KIDNEY INJURY

Sirtuin 3—a master regulator of mitochondrial integrity in AKI

Sirtuin 3 (SIRT3) protects against acute kidney injury (AKI) by preserving mitochondrial integrity and could be a target for improving outcomes of patients with AKI, say researchers. "Pharmacological manipulations that increase SIRT3 improve renal function and decrease tubular injury in mice," explains researcher Ariela Benigni. "Moreover, our studies in cultured human tubular epithelial cells (TECs) demonstrate a functional role of SIRT3 in regulating mitochondrial dynamics in AKI."

Previous studies had demonstrated that SIRT3—the predominant mitochondrial deacetylase—reduces levels of reactive oxygen species, which are known to contribute to mitochondrial damage and tubular injury in experimental AKI. To investigate the role of SIRT3 in AKI, Benigni and co-workers first assessed the effects of AKI on SIRT3 expression. Mice with cisplatin-induced AKI had reduced expression of renal SIRT3; administration of the AMPK agonist AICAR or the antioxidant ALCAR increased SIRT3 levels, ameliorated tubular damage and improved renal function in wild-type, but not in SIRT3-deficient mice.

In cultured human TECs, cisplatin treatment also reduced SIRT3 levels, causing mitochondrial fragmentation. AICAR and ALCAR restored *SIRT3* levels in wild-type TECs but not in TECs in which *SIRT3* had been silenced. By contrast, transfection of *SIRT3* protected mitochondria from cisplatin-induced fragmentation, membrane depolarization and organelle fission.

"Our study shows for the first time that SIRT3 is a master regulator of mitochondrial integrity in AKI," says Benigni. "The obvious translational step is to now look for potential SIRT3-activating compounds."

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Original article Morigi, M. *et al*. Sirtuin 3-dependent mitochondrial dynamic improvements protect against acute kidney injury. *J. Clin. Invest*. doi:10.1172/JCI77632