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ACUTE KIDNEY INJURY

Improved fuel metabolism protects against AKI

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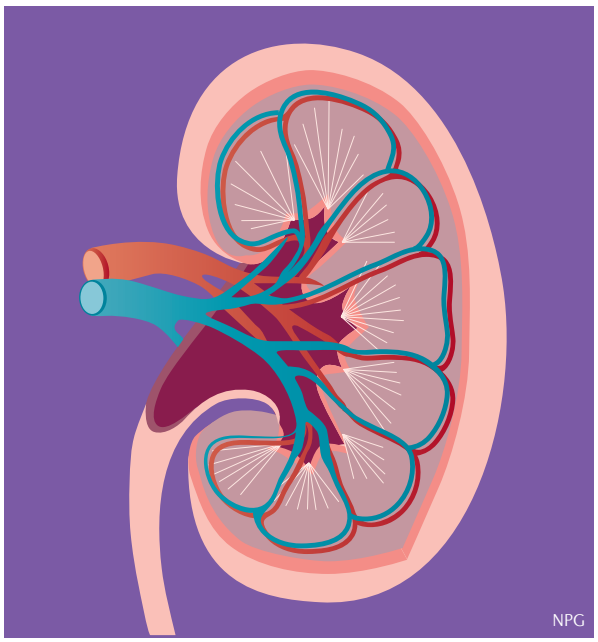
The kidney is a highly metabolic organ with an abundance of mitochondria. Mitochondrial dysfunction contributes to the pathophysiology of tissue injury in acute kidney injury (AKI), but the mechanisms involved are unclear. New findings identify the mitochondrial biogenesis regulator, PGC1α, as a key determinant of renal recovery from AKI by regulating the production of nicotinamide adenine dinucleotide (NAD) and prostaglandin E2. "Leaders in renal biology have provided tremendous inspiration for our work," says senior researcher Samir Parikh. "The importance of mitochondria and prostaglandins in the pathogenesis of AKI has been eloquently articulated for decades; our studies simply bring these two major strands of research together. More fundamentally, PGC1α and NAD have been separately implicated in stress resistance, particularly as they relate to ageing; our studies draw a direct line from PGC1α to NAD."



Previous work by the researchers identified involvement of PGC1α, a major regulator of mitochondrial biogenesis and metabolism, in resistance to and recovery from sepsis-associated AKI. In the current study, Parikh and colleagues show that renal ischaemia–reperfusion injury (IRI) leads to a decline in PGC1α levels in association with renal dysfunction, swollen tubular mitochondria and an increase in acylglycerols, indicative of altered fuel metabolism. To further investigate the role of PGC1α and mitochondrial function in AKI, the researchers generated genetic mouse models to assess the effects of PGC1α deficiency and overexpression on AKI outcomes. "We hypothesized that PGC1α could be an important determinant of renal stress resistance in diverse contexts," explains Parikh. "One of our goals has been to identify mechanisms that unite some of the many different AKI syndromes such as sepsis-mediated or ischaemia-induced AKI."

Following IRI, mice deficient in PGC1α experienced worse outcomes than those of control mice, with more tubular injury, worse renal function and a greater accumulation of fat. Metabolite profiling revealed a deficiency of the NAD precursor niacinamide (NAM) in PGC1α$^{-/-}$ mice; administration of NAM to these mice prevented post-ischaemic AKI and fat accumulation, identifying NAM as a functional downstream effector of PGC1α. Mice that overexpressed PGC1α in tubular epithelial cells had higher levels of NAM and better renal outcomes following IRI and endotoxin-induced nephropathy than did control mice. "It was important to not only determine that loss of PGC1α exacerbated injury, but also to ask whether increasing the renal tubular levels of PGC1α conversely promoted resistance to injury, which is critical when thinking about ways to help people resist AKI-inducing stressors," explains Parikh. "Once we had results supporting our hypothesis, the next question was how this could all be working."

To examine the mechanisms by which PGC1α and NAM protect against AKI, Parikh and his collaborators used metabolomics and RNA sequencing to identify a set of downstream metabolic targets. "We found evidence that PGC1α in the renal tubule affects fuel metabolism by modulating levels of the energy carrier NAD," explains Parikh. "In turn, better fuel metabolism promoted the production of the fatty acid breakdown product β-hydroxybutyrate and the renoprotective prostaglandin E2."

Parikh says that many questions remain unanswered, such as the mechanisms by which PGC1α regulates the biosynthesis of NAD and how different cellular stress conditions affect this pathway. The researchers also hope to examine whether traditional risk factors for AKI affect the PGC1α–NAD axis.

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ORIGINAL ARTICLE Tran, M. T. *et al.* PGC1α drives NAD biosynthesis linking oxidative metabolism to renal protection. *Nature* http://dx.doi.org/10.1038/nature17184
FURTHER READING Emma, F. *et al.* Mitochondrial dysfunction in inherited renal disease and acute kidney injury. *Nat. Rev. Nephrol.* http://dx.doi.org/10.1038/nrneph.2015.214