Renal oxygen consumption is directly proportional to solute extraction, an observation reported over 80 years ago [1]. The electrochemical force for solute extraction is generated primarily by abundant mitochondria found in the proximal tubule and thick ascending limb. Genetic and acquired mitochondrial disorders conclusively demonstrate that injury to this organelle impairs tubular, and indeed, global renal function [2]. But what role does the mitochondrion, and energy metabolism more broadly, play in the development of acute kidney injury (AKI)? This question is too broad to cover here and therefore, this mini-review will focus on one aspect: new findings that link mitochondrial biogenesis to nicotinamide adenine dinucleotide (NAD+) biosynthesis.

PPARγ-coactivator-1α (PGC1α) is highly expressed in metabolically active organs including brown fat, the heart, brain, skeletal muscle, liver, and kidney [3, 4]. It binds to an array of transcription factors, driving the expression of hundreds of genes that, collectively, increase metabolic health and the ability to resist renal stressors.
cellular mitochondrial abundance [5]. Renal PGC1α expression is largely restricted to cell types with abundant mitochondria that are found in the tubule [6]. Vascular and podocyte expression of PGC1α is comparatively low. Germline PGC1α deletion is nonlethal. Animals have slightly reduced baseline mitochondrial abundance. But PGC1α appears to be important for the defense against stressors in these organs [7–9]. During experimental and human AKI, renal PGC1α expression falls [6, 10, 11]. This change in expression does not drive the mitochondrial pathology of AKI per se but does impair the cell’s ability to respond adaptively. Global or tubule-specific knockout mice are more susceptible to septic and ischemic AKI [6, 11]. Conversely, the genetic induction of PGC1α in the tubule protects against either. Excess PGC1α restores the energy metabolism and ATP generation that is otherwise impaired by cytokines or oxidant stress [6, 12]. Excess tubular PGC1α reduces the severity of AKI and accelerates functional resolution [11].

To understand how PGC1α impacts renal metabolism in AKI, Tran et al. [11], applied RNA sequencing and metabolomics to post-ischemic kidneys, PGC1α knockout kidneys, and PGC1α transgenic kidneys. These systems biology studies led them to consider Nam, a metabolite produced by the kidney that is the chief precursor for NAD+. NAD+ is a universal electron carrier that is required for oxidation of glucose and fats [13, 14]. NAD+ is rate-limiting for oxidative metabolism [15]. Renal Nam and NAD+ levels are strongly intercorrelated. Both fall during AKI, with NAD+ declining to a similar extent as ATP itself. Both are reduced at baseline in PGC1α knockout kidneys, whereas both are elevated at baseline in transgenic kidneys. PGC1α coordinately regulates an 8-step enzymatic pathway for the de novo biosynthesis of NAD+. NAD+ reduction in AKI may reflect both a PGC1α-dependent impairment of biosynthesis and excessive degradation by enzymes known to promote AKI [16].

Exogenous Nam boosts renal NAD+, normalizes the heightened post-ischemic response of PGC1α knockout mice, prevents toxic AKI induced by cisplatin, and rescues early post-ischemic AKI. These striking results propose that AKI constitutes a state of acute NAD+ deficiency that can be therapeutically targeted by NAD+ augmentation [11]. Independent results with the immediate downstream intermediate between Nam and NAD+, Nam mononucleotide, further support the possibility of therapeutic NAD+ augmentation in multiple etiologies of AKI [17]. There may be several effectors of renal tubular defense downstream of NAD+. For example, the induction of fatty acid metabolism may resolve incipient lipotoxicity and promote the accumulation of beta-hydroxybutyrate, a ketone body that signals the production of the renoprotective prostaglandin PGE2 [11, 18]. Left unchecked, deranged fat metabolism may be profibrotic [18]. NAD+ serves as a cofactor for sirtuin enzymes that have been linked to renoprotection [17, 19, 20]. Finally, NAD+ augmentation can boost mitochondrial function and enhance mitophagy [21]. While downstream effectors of renal NAD+ will require further study (Fig. 1), the emerging body of work suggests that PGC1α-induced defense of NAD+ levels may be critical for renal stress resistance.

If the PGC1α-NAD+ axis is important for AKI pathogenesis, then several translational avenues merit investigation. Renal biopsy studies show the suppression of this axis in renal disease, so new ways to assess PGC1α-NAD+ status by simple blood or urine tests could be beneficial. Related to this, AKI risk stratification currently accounts for age and chronic kidney disease (CKD) and both of these contexts are associated with reductions in PGC1α and NAD+, suggesting that new diagnostic tools could unveil underlying biological factors connecting aging to acute and chronic renal disease. Such "metabolic" risk stratification could help individualize management decisions. For future therapeutics, upstream targeting of PGC1α has been challenging; yet several compounds boost NAD+, including Nam itself. Defining the best contexts for clinical evaluation – for example, perioperative
AKI, toxic exposures, or septic shock – will require careful thought. These challenges notwithstanding, recent work has unveiled novel metabolic underpinnings of renal disease. As PGC1α and NAD+ may lie at the nexus of aging, CKD, and AKI, these discoveries present new opportunities to stratify risk, individualize management, and treat patients in a targeted way.

Acknowledgments and Disclosure Statement

The authors were unable to cite numerous contributions due to space limitations. S.M.P. is supported by DK-095072. A.P.M. is supported by an Innovation Grant at BIDMC. S.M.P. is listed as inventor on filings related to PGC1α and NAD+ submitted by BIDMC. S.M.P. has consulted for Merck. Otherwise, there are no conflicts to disclose.

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PGC1α, NAD+ and Renal Stress Resistance
Nephron 2017;137:253–255
DOI: 10.1159/000471895

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