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**Commentary**

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# The role of Sirt1 in renal rejuvenation and resistance to stress

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**This issue of the *JCI* includes studies demonstrating that sirtuin 1 (Sirt1), a NAD<sup>+</sup>-dependent deacetylase, slows renal senescence and safeguards cells in the renal medulla. Kume et al. demonstrated that caloric restriction protected the aging kidney by preserving renal Sirt1 expression, the latter deacetylating forkhead box O3a (FOXO3a), inducing Bnip 3, and promoting mitochondrial autophagy. Sirt1 expression, as shown by He et al., enabled interstitial cells to withstand the oxidizing medullary environment and exerted antiapoptotic and antifibrotic effects in the obstructed kidney. Sirt1 is thus an important participant in renal cytoprotective responses to aging and stress.**

The regulation of salt and water balance is one of the salient contributions of the kidney to the preservation of the constancy of the internal environment. Each day some 26,000 mmol of sodium and 180 liters of water traverse the glomerular filtration barrier into the urinary space, and all but 1% of such filtrate is faithfully returned by the tubular epithelium to the vascular compartment. Renal sodium reabsorption requires ATP, and to generate sufficient amounts of ATP for sodium transport, the kidney avidly consumes oxygen to drive mitochondrial oxidative phosphorylation; indeed, oxygen consumption/tissue weight by the kidney is exceeded, among major organs, only by the beating heart (1). A small percentage of oxygen consumed by mitochondria is incompletely reduced to reactive oxygen species (ROS), and this unremitting generation of oxidants during mitochondrial respiration, albeit in small amounts, may cumulatively take its toll on organs such as the kidney that are heavily dependent on mitochondrial metabolism.

## Caloric restriction delays renal senescence via Sirt1

The mitochondrial theory of aging posits that mitochondrial ROS target DNA and other mitochondrial components, and such oxidative modifications impair the electron transport chain, with an attendant augmen-

tation in mitochondrial generation of ROS; a self-perpetuating cycle of mitochondria-based oxidative injury then ensues, leading to the progressive failure of bioenergetics and other aspects of mitochondrial function (2). This pathogenetic cascade may be interrupted in aging organs if injured mitochondria can first be culled and cordoned off from relatively healthy mitochondria and then selectively digested and reabsorbed. Such autophagy, as shown in the study reported by Kume et al. in this issue of the *JCI*, underlies the salutary effects of caloric restriction on the aging murine kidney and is actuated by sirtuin 1 (Sirt1) (3). Through its NAD<sup>+</sup> deacetylase activity, Sirt1 can deacetylate a number of targets, including the transcription factor forkhead box O3a (FOXO3a). When deacetylated, and under the hypoxic conditions studied by Kume et al., FOXO3a promoted the expression of *Bnip3*, a gene that enables autophagy to occur. However, when FOXO3a remained acetylated, its transcriptional activity switched from *Bnip3* to *Bim1*, the latter facilitating apoptosis. Thus, the age-dependent decline in Sirt1 activity in mice fed ad libitum, as observed by Kume et al., elicited transcriptional behavior of FOXO3a directed toward cell death (3). In contrast, caloric restriction, a dietary manipulation that promotes longevity, abrogated the reduction in renal Sirt1 expression that occurred with age; consequently, the transcriptional activity of FOXO3a was geared toward the selective disposal of damaged mitochondria by autophagy, rather than the loss of kidney cells by apoptosis (Figure 1). In the aging

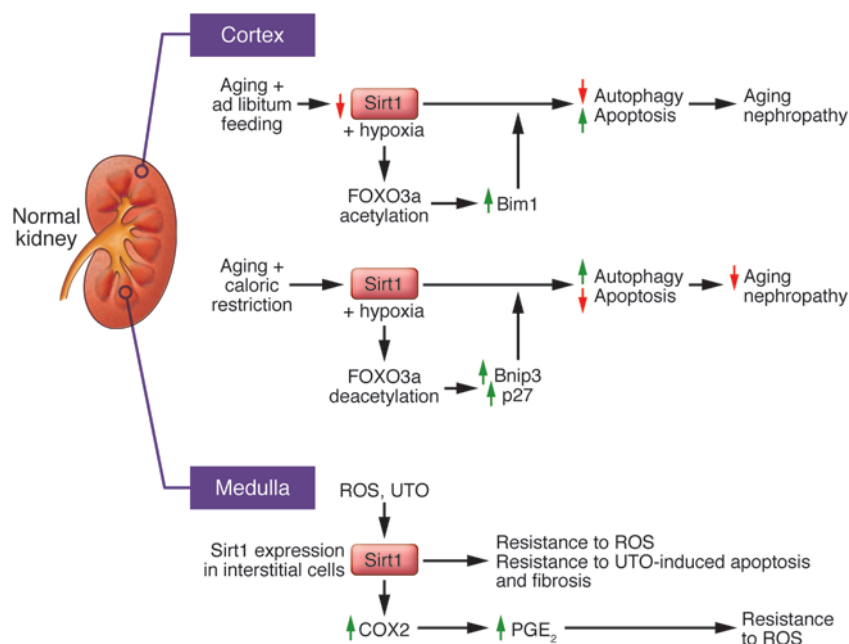
kidney, caloric restriction concomitantly reduced oxidative stress, preserved the population of healthy mitochondria, lessened fibrosis, and improved renal function (3).

Kume et al. uncovered the basis for the protective effects of Sirt1 in proximal tubular epithelial cells exposed, under hypoxic conditions, to serum from rodents maintained on caloric restriction; such serum can recapitulate in vitro effects observed with caloric restriction in vivo (3). The rationale for subjecting proximal tubular cells to hypoxia rests on the development of hypoxia in the aging renal cortex (3, 4) and the implication of hypoxia in the pathogenesis of aging nephropathy (4). Additionally, hypoxia can promote mitochondrial generation of ROS and thus may contribute to the cycle of mitochondrial oxidant stress and injury (5). Moreover, as observed by Kume et al., caloric restriction reduced renal injury without alleviating cortical hypoxia (3). In their in vitro studies, they demonstrated that the instigation of the Sirt1-deacetylated FOXO3a pathway by caloric restriction recruited not only *Bnip3* but also p27, a cyclin-dependent kinase inhibitor (3). While the cell cycle-inhibitory effects of p27 may contribute to the salutary effects of caloric restriction, p27 exerts antiapoptotic effects in the kidney (6), and such actions of p27 may also be relevant. Thus, cell cycle-related and antiapoptotic processes, along with mitochondrial autophagy, were utilized by the Sirt1-deacetylated FOXO3a pathway in mediating the beneficial effect of caloric restriction on renal aging.

The deacetylating activity of Sirt1 also mediates hypoxia-induced activation of HIF-2 $\alpha$  (7), a transcription factor that regulates expression of erythropoietin, and angiogenic and antioxidant genes (8). Interestingly, the renal cortical interstitium in aged rodents expresses significant amounts of HIF-2 $\alpha$  (4), and thus the effect of caloric restriction on HIF-2 $\alpha$  in the aging kidney would be of interest. The findings of Kume et al. (3) are also relevant to chronic kidney

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**Figure 1**

Sirt1 plays an important role in renal cytoprotective responses to aging and stress. In this issue of the *JCI*, Kume et al. (3) demonstrated that in aged mice maintained on ad libitum feeding, the kidney exhibited cortical hypoxia and decreased expression of Sirt1; caloric restriction prevented the reduction in Sirt1 but did not alleviate cortical hypoxia. Transcriptional targets of acetylated FOXO3a include Bim1, while those of deacetylated FOXO3a include Bnip3 and p27. In the medulla, as reported by He et al. in this issue (15), interstitial cells expressed Sirt1; Sirt1 conferred resistance to urinary tract obstruction-induced (UTO-induced) apoptosis and fibrosis and to ROS, in part, through the expression of COX2 and PGE<sub>2</sub> (15).

disease, since cortical hypoxia is increasingly implicated in the pathogenesis of chronic kidney disease (9–11). There is substantial interest in strategies that alleviate hypoxia or its attendant effects as a way of retarding chronic kidney disease. The studies by Kume et al. emphasize that altering the response to hypoxia, rather than hypoxia itself, may protect impressively against renal injury (3).

### The inimical milieu of the renal medulla

Hypoxia also exists in the renal medulla, but whereas the renal cortex requires aging or chronic kidney disease to become hypoxic, hypoxia is a constant and defining feature of the medulla in the healthy kidney (1, 12–14). The renal medulla critically contributes to overall renal function, as it reabsorbs substantial amounts of filtered sodium, regulates water excretion, and assists in the maintenance of normotension. Such functioning of the medulla occurs despite the presence of hypoxia and other conditions that threaten cell viability, and these include a meager blood supply, increased ammonia concentrations, substantial ROS generation by a metabolically active thick ascending limb, and markedly increased interstitial osmolality (1, 12, 13). Interstitial hyperosmolality, due to the high interstitial concentrations of sodium chloride and urea, may perturb cellular structure and function, in part, by promoting the generation of ROS. Cells can only

survive and function in such an inhospitable environment if they possess innate mechanisms that safeguard their vitality.

### Sirt1 as an endogenous protectant in the medulla

One such mechanism, as shown in the study reported in this issue by He et al., involved cellular expression of Sirt1 (15). Their studies demonstrated that the medulla was enveloped in oxidative stress and Sirt1 was prominently expressed by medullary interstitial cells (15). Sirt1 protected against oxidant-induced injury to medullary interstitial cells in vitro, and in an in vivo model of oxidative stress imposed by obstructive nephropathy, Sirt1 reduced apoptosis and interstitial fibrosis that occurred in the medulla (Figure 1). In exploring the basis for these effects of Sirt1, He et al. recognized that the Sirt1-expressing cells also expressed COX2. Furthermore, Sirt1 mediated the induction of COX2, which occurred in the obstructed kidney and upon exposure to ROS. Finally, one of the products of COX2, PGE<sub>2</sub>, accounted, in part, for the cytoprotective effects of Sirt1 (15).

### Pathophysiologic implications of medullary expression of Sirt1

The observations of He et al. (15) are relevant to a number of pathophysiologic issues. First, COX2/PGE<sub>2</sub> contributes to the anti-hypertensive actions of the renal medulla by increasing medullary blood flow and sodium excretion (14, 16); renal

expression of Sirt1, by inducing COX2/PGE<sub>2</sub>, may thus modulate, directly, intrarenal hemodynamics and, indirectly, systemic hemodynamics. Second, aging impairs renal regulation of salt and water balance and is associated with systemic hypertension (17); these age-related effects may reflect, in part, medullary dysfunction incurred by an age-related decline in medullary expression of Sirt1. Third, the protection conferred by induced Sirt1 in the obstructed kidney raises the possibility that a similar scenario may also occur in ischemic, inflammatory, and other types of renal injury. Finally, these findings are germane to chronic kidney disease. Irrespective of the cause of chronic kidney disease, tubulointerstitial disease develops in the cortex, and the severity of such tubulointerstitial disease determines the decline in renal function (18). Since cortical expression of Sirt1 is lower than that in the medulla (15), the cortex may thereby be vulnerable to the initiation and progression of tubulointerstitial disease.

### Conclusions

The studies reported by Kume et al. (3) and He et al. (15) in this issue of the *JCI* identify Sirt1 as a new and important participant in the repertoire of renal cytoprotective responses. Such observations thus advance our understanding of the nature and range of renal responses to stress and aging (19, 20). Moreover, these studies open up an investigative path that leads to the explora-



tion of Sirt1 as a protectant against other clinically relevant renal insults, and an investigative path that would culminate, hopefully, in the discovery of novel therapies for human kidney disease.

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- Schoolwerth A, Drewnowska K. Renal Metabolism. In: Schrier R, Gotschalk C, eds. *Diseases of the Kidney*. New York, NY: Little, Brown and Company; 1997:203–230.
- Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. *Cell*. 2005;120(4):483–495.
- Kume S, et al. Calorie restriction enhances cell adaptation to hypoxia through SIRT1-dependent mitochondrial autophagy in mouse aged kidney. *J Clin Invest*. 2010;120(4):1043–1055.
- Tanaka T, et al. Hypoxia and expression of hypoxia-inducible factor in the aging kidney. *J Gerontol A Biol Sci Med Sci*. 2006;61(8):795–805.
- Chandel NS, Budinger GR. The cellular basis for diverse responses to oxygen. *Free Radic Biol Med*. 2007;42(2):165–174.
- Hirohara K, Pippin JW, Fero ML, Roberts JM, Shankland SJ. Modulation of apoptosis by the cyclin-dependent kinase inhibitor p27(Kip1). *J Clin Invest*. 1999;103(5):597–604.
- Dioum EM, et al. Regulation of hypoxia-inducible factor 2alpha signaling by the stress-responsive deacetylase sirtuin 1. *Science*. 2009;324(5932):1289–1293.
- Guarente L. Cell biology. Hypoxic hookup. *Science*. 2009;324(5932):1281–1282.
- Fine LG, Norman JT. Chronic hypoxia as a mechanism of progression of chronic kidney diseases: from hypothesis to novel therapeutics. *Kidney Int*. 2008;74(7):867–872.
- Haase VH. Oxygen regulates epithelial-to-mesenchymal transition: insights into molecular mechanisms and relevance to disease. *Kidney Int*. 2009;76(5):492–499.
- Tanaka T, Nangaku M. The role of hypoxia, increased oxygen consumption, and hypoxia-inducible factor-1 alpha in progression of chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2010;19(1):43–50.
- Neuhofer W, Beck FX. Survival in hostile environments: strategies of renal medullary cells. *Physiology (Bethesda)*. 2006;21(1–4):171–180.
- Burg MB, Ferraris JD, Dmitrieva NI. Cellular response to hyperosmotic stresses. *Physiol Rev*. 2007;87(4):1441–1474.
- Cowley AW Jr. Renal medullary oxidative stress, pressure-natriuresis, and hypertension. *Hypertension*. 2008;52(5):777–786.
- He W, et al. Sirt1 activation protects the mouse renal medulla from oxidative injury. *J Clin Invest*. 2010;120(4):1056–1068.
- Hao CM, Breyer MD. Physiological regulation of prostaglandins in the kidney. *Annu Rev Physiol*. 2008;70:357–377.
- Rosenthal T, Shamiss A, Holtzman E. Dietary electrolytes and hypertension in the elderly. *Int Urol Nephrol*. 2001;33(3):575–582.
- Nath KA. Tubulointerstitial changes as a major determinant in the progression of renal damage. *Am J Kidney Dis*. 1992;20(1):1–17.
- Nath KA. Heme oxygenase-1: a provenance for cytoprotective pathways in the kidney and other tissues. *Kidney Int*. 2006;70(3):432–443.
- Schmitt R, Cantley LG. The impact of aging on kidney repair. *Am J Physiol Renal Physiol*. 2008;294(6):F1265–F1272.

## The one-two punch: knocking out angiotensin II in the heart

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**Ang II plays an important role in the pathophysiology of cardiovascular disease. Angiotensin-converting enzyme (ACE) inhibitors lower Ang II levels by inhibiting conversion of Ang I to Ang II, but Ang II levels have been shown to return to normal with chronic ACE inhibitor treatment. In this issue of the JCI, Wei et al. show that ACE inhibition induces an increase in chymase activity in cardiac interstitial fluid, providing an alternate pathway for Ang II generation.**

Despite ongoing advances in modern medicine, cardiovascular disease (CVD) remains a major cause of death. Ang II has been implicated in the pathophysiology of atherosclerosis and heart failure (HF) due to its role in regulating multiple renal and cardiovascular functions, including salt/water retention, vasoconstriction, aldosterone secretion, cardiac hypertrophy, thrombosis, fibrosis, and others (1). In the classical renin-angiotensin system (RAS), angiotensinogen (AGT) produced in the liver enters the circulation,

where it is cleaved by renin produced in the kidneys to form Ang I. Ang I is converted to Ang II by angiotensin-converting enzyme (ACE) bound to vascular endothelial cells. Ang II then binds to either the Ang II type 1 receptor (AT1), through which it exerts most of its known effects, or to the Ang II type 2 receptor (AT2), which is thought to oppose AT1 (2). However, research conducted over the last few decades has shown that the RAS is much more complex in both mechanism and effect than once thought (Figure 1).

Some of this complexity comes from the discovery of nonclassical RAS components. Although Ang II is generally considered to be the main RAS effector molecule, other Ang peptides have been discovered, including

Ang-(1–7), Ang-(1–9), Ang-(2–8), Ang-(3–8), and Ang-(1–12) (2, 3). In particular, Ang-(1–7) opposes the effects of Ang II through binding to the Mas receptor (3) and inhibits bradykinin (BK) degradation, possibly through competitive binding to ACE (4), while Ang-(1–12) is an alternative precursor for Ang I and II generation (3). In addition, other enzymes cleave AGT and its products. Cathepsin, like renin, generates Ang I from AGT (5), ACE2, an ACE homolog, and neutral endopeptidases cleave Ang I and II to form Ang-(1–7) (2, 6), and some chymases efficiently cleave Ang I to produce Ang II (7) and may be responsible for generation of Ang II from Ang-(1–12) (3). Furthermore, both ACE and chymase have additional functions besides Ang peptide cleavage. ACE is also a kininase (8), linking the RAS and the kallikrein/kinin system, while chymase activates procollagenase and MMPs and catalyzes degradation of thrombin and plasmin, playing an important role in tissue remodeling (7).

How and when these various components come into play depends on the context.

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