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Mitochondrial ROS deficiency and diabetic complications: AMP[K]-lifying the adaptation to hyperglycemia

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Global, sustained production of ROS has deleterious effects on tissue structure and function and gives rise to biochemical and physiological changes associated with organ senescence. Specific, localized ROS metabolites generated by mitochondria and NADPH oxidases also transduce homeostatic information in response to metabolic, mechanical, and inflammatory cues. In this issue of the *JCI*, Dugan and colleagues demonstrate that mitochondrial-derived ROS, which is maintained by a feed-forward AMP kinase activation cascade, is reduced in diabetes and plays an adaptive role in preserving renal glomerular function during hyperglycemia. This enlightened view of mitochondrial ROS biology forces us to reconsider therapeutic approaches to metabolic disease complications such as diabetic nephropathy.

Diabetes management: a complicated issue

With an estimated 366 million individuals afflicted worldwide, the importance of diabetes' effects on human health and healthcare cannot be overstated (1). In the United States alone, the direct and indirect costs are staggering. Every year in the US, 250 billion dollars, approximately 1.5% of the country's entire gross domestic product, is spent on diabetes and its complications (2). The intrinsic cellular responses and vascular injury that arise from hyperglycemia result in a variety of costly complications such as neuropathies, retinopathies, and cardiovascular disease, which includes heart failure, stroke, myocardial infarction, and arteriosclerosis. Improvements in glycemic control alone are insufficient to fully mitigate diabetes-associated complications; therefore, clinical differences in the pathobiology of diabetic end organ complications should drive the search for adjunctive therapeutic approaches above and beyond glycemic control. For example, intensive control of both glucose and lipid intake has emerged as an effective strategy for reducing retinopathy (3), but other diabetes-associated complications such as nephropathy (4) and macrovascular disease (5) remain refractory to this focused metabolic strategy. Moreover, interactions between the metabolites produced in association with diabetes and chronic kidney disease synergize and have devastating effects on cardiovascular health (6). Innovative therapeutic approaches are necessary for diabetes treatment, and the pathways involved in mitochondrial oxidative stress have become attractive targets (7).

Oxidative stress in diabetes

It is widely appreciated that extracellular oxidative stress globally increases in both type 1 diabetes (T1D) and type 2 diabetes (T2D) (8, 9). Current opinion holds that diabetes-associated mitochondriopathy (7) directly contributes to ROS generation, as has been observed in isolated endothelial cells (10). ROS and oxylipid metabolites are critical for the microbiocidal activity of phagocytes, wound healing, and the pathobiology of several inflammatory diseases including atherosclerosis. Since ROS can induce DNA damage and both are increased in diabetes (11, 12), the accumulation of both diabetes-associated mitochondrial and genomic DNA alterations are considered to be the consequence of abnormal mitochondrial ROS production. Multiple cellular enzymes generate ROS signatures in distinct subcellular venues (13), primarily superoxide (e.g., NOX1, NOX2, mitochondrial complexes), with rapid dismutation to H_2O_2 or direct H_2O_2 elaboration (e.g., NOX4, acyl-CoA oxidase, xanthine oxidase). These local intracellular ROS signatures, which are dynamic and elicited in response to intracellular and extracellular cues, are highly regulated and critical second messengers in metabolism and signal transduction (14). The interrelationships between distinct intracellular ROS metabolism and extracellular oxidative stress are poorly understood but are of emerging importance in the pathogenesis of organ dysfunction associated with aging and chronic diseases including diabetes (14).

In this issue of the *JCI*, Dugan and colleagues examine the role of mitochondrial-derived superoxide in diabetic kidney disease (15). Implementing multiple validated and unconventional methods of superoxide assessment, they demon-

Conflict of interest: The author has declared that no conflict of interest exists.

Citation for this article: *J Clin Invest.* 2013; 123(11):4573–4576. doi:10.1172/JCI72326.

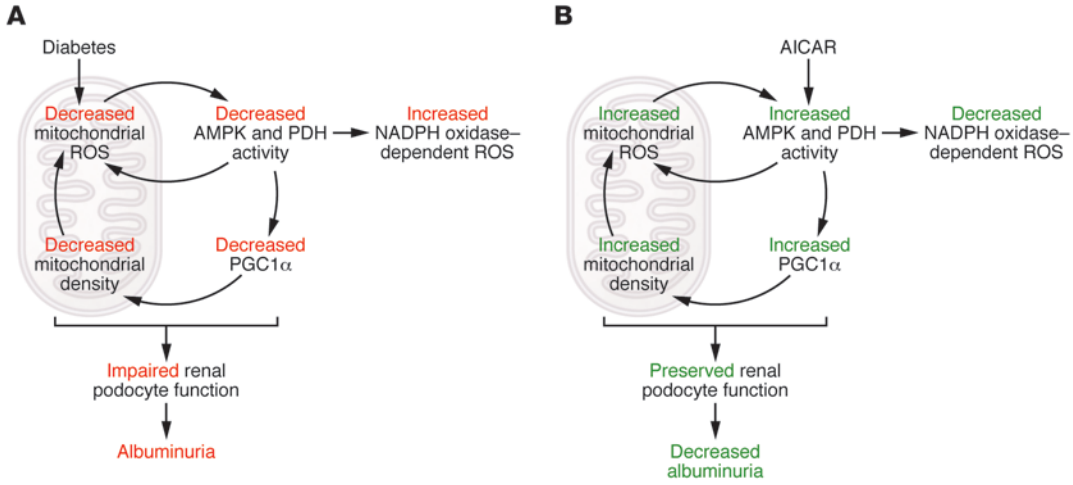

Figure 1
A feed-forward cycle of AMPK-activated mitochondrial metabolism and ROS generation by the kidney reduces diabetes-induced albuminuria. (**A**) Diabetes results in decreased renal mitochondrial superoxide production, which is associated with decreased AMPK and PDH activity. Decreases in AMPK and PDH activity further reduce mitochondrial ROS production directly and through decreased PGC1α, which promotes decreased mitochondrial density, ultimately resulting in impaired renal podocyte function and albuminuria. Decreased AMPK also results in increased NADPH oxidase–dependent ROS production. (**B**) Restoration of renal mitochondrial ROS production by treatment with the AMPK activator AICAR reduces albuminuria and total renal oxidative stress. Mitochondrially derived ROS, which is stimulated by AICAR and amplified by a feedforward AMPK cascade, is protective in the setting of hyperglycemia. The failure of mitochondrial ROS generation contributes to diabetic kidney disease. Furthermore, AMPK activation reduces NADPH oxidase–dependent ROS formation.

strate that renal mitochondria in two models of T1D (streptozotocin-treated [STZ-treated] mice and *Ins2*^{Akita} mice) produced reduced levels of superoxide even though total urinary ROS were increased. Diabetes-associated reductions in mitochondrial ROS resulted in the concomitant downregulation of the redox sensor AMPK along with reduced pyruvate dehydrogenase (PDH) activity and proliferator-activated receptor γ coactivator 1 α (*Pgc1α*) expression (Figure 1). Deficiencies in PGC1α expression and activity presumably contribute to diabetes-associated reductions in total mitochondrial density (16, 17). Even though mitochondrial ROS was reduced in diabetes, mitochondrial DNA (mtDNA) damage was increased and fully uncoupled from mitochondrial oxidative stress (15). Importantly, mtDNA damage was directly related to the diabetic state in both *Ins2*^{Akita} and STZ-treated mice and unrelated to possible chemical alkylation from STZ treatment (Figure 1). Administration of the AMPK activator 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) (18) reversed AMPK inhibition, which restored renal mitochondrial numbers, ROS elaboration (15), and PGC1α induction, and reduced tissue mtDNA fragmentation (Figure 1). It is unclear how AMPK activation reduces mtDNA damage, but it likely involves enhanced mitochondrial biogenesis (via PCG1α) as well as mitochondrial turnover/mitophagy (19, 20). Albuminuria, which is a clinically relevant index of diabetic nephropathy and renal podocyte dysfunction (21), developed in both STZ and *Ins2*^{Akita} T1D models and was reversed by AICAR administration (15). Finally, the authors found that renal albumin responses to AICAR were lost in mice lacking AMPK, confirming that the relief of diabetic complications by AICAR is mediated via AMPK activation. Of note, AICAR treatment globally reduced renal ROS formation while simultaneously promoting mitochondrial superoxide generation (15). These data indicate that renal mitochondrial-derived ROS are not the major source of renal oxidative stress in diabetes. This leads to a somewhat iconoclastic concept: mitochondrial-derived renal ROS, which are stimulated by AICAR and amplified by a feed-forward AMPK cascade (Figure 1), are protective in a hyperglycemic setting, and failure of mitochondrial ROS generation contributes to diabetic kidney disease (15).

Reexamining the role of ROS and other diabetes-associated metabolites

Why is this study important? It forces us to reexamine our understanding of diabetic nephropathy and pathobiology as well as several other diabetes- and aging-related complications. A more detailed understanding of the mechanisms underlying diabetes-induced mtDNA damage is needed, since this antecedent genomic alteration likely contributes to impaired mitochondrial function (Figure 1). The role of mitochondria as sophisticated signaling organelles must be carefully considered when crafting diabetes-related treatment strategies (14, 22). In addition to ROS, several non-ROS metabolites that are regulated by hyperglycemia, PDH activation, and mitochondrial carbon flux, such as succinate and α-ketoglutarate, are ligands for G protein–coupled receptors found in the kidney (23, 24). Certainly, the indiscriminate "scavenging" of cellular ROS as a therapeutic approach to chronic disease may not be logical given the important role of cellular H_2O_2 as a second messenger in both adaptive and maladaptive responses (14). The concepts and pathways identified in ischemic preconditioning, which is a process that activates AMPK as a component of myocardial protection to subsequent hypoperfusion (25, 26), may be applicable to early diabetic kidney disease. Since mitochondrial ROS signaling couples NADPH oxidase/NOX activation with prosclerotic responses in renal mesangial cells, vascular smooth muscle cells, arte-

rial myofibroblasts, and cardiomyocytes (27–30), the details of cell-type specificity will be important as we unravel how temporospatial alterations in ROS generation affect diabetic complications (8, 14). Additionally, the net effect of enhanced mitochondrial ROS production in one organ may dramatically differ depending on the phase of disease. For example, ROS may differentially affect events associated with diabetes initiation, such as early epithelial podocyte injury, compared with progressive complications such as advancing glomerulosclerosis (31–34).

Some challenges exist as we seek to optimally integrate these important insights into the development of therapeutic approaches to patient care. For example, mitochondrial-derived ROS participate in the vascular calcification characteristic of diabetes, uremia, and hyperphosphatemia (35). The onset of vascular calcification is related in part to the recruitment of prosclerotic signaling cascades downstream of NADPH oxidase, NOX, and NF-κB activation (36). Thus, indiscriminate activation of mitochondrial ROS signals is likely an important pitfall to avoid. Importantly, AMPK activity suppresses NOX activation (37) while sustaining mitochondrial ROS tone (15), thereby, uncoupling these two cellular ROS pathways (Figure 1). A strategy that mimics this bipartite action of AMPK activation is most likely to convey renal benefit and concomitantly mitigate arteriosclerotic vascular stiffening. An inconvenient truth that was elucidated by Zou and colleagues is that AMPK α2 activation downstream of nicotine exposure engenders aneurysm formation (38). Thus, the Aristotelian call for moderation in all things will likely apply to therapeutics targeting AMPK isoforms or upstream activators (20). Since AMPK isoforms α1 and α2 differ in cell specificity, sensitivity to ROS activation, and impact on aneurysmal remodeling, strategies that selectively target these two catalytic isoforms or their β/γ regulatory subunits may afford unique therapeutic windows (20). This potentially promising strategy has yet to be pharmacologically explored (39, 40), but has yet to be pharmacologically exploited. Moreover, in the setting of chronic kidney disease, metabolomic strategies that interrogate and integrate renal epithelial secretory and glomerular filtration functions (41) with mitochondrial metabolic markers including oxylipids (42) should be informative and guide stage-specific treatment decisions for any AMPK modulator (41). All in all, the insights afforded by the elegant study of Dugan and colleagues (15) are truly exciting and will no doubt prove extremely useful as we craft new therapeutic strategies to mitigate or prevent the end-organ complications arising in our patients with diabetes (1, 2).

Acknowledgments

D.A. Towler is supported by grants HL069229, HL081138, and HL114806 from the NIH, and the Sanford-Burnham Medical Research Institute.

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Regulatory T cells use "*Itch*" to control asthma

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Regulatory T cells (Tregs) control type 2 T helper cell–mediated (Th2-mediated) lung inflammation, but the molecular mechanisms by which Tregs execute this activity remain elusive. In this issue of the *JCI*, Jin et al. reveal that Itch, a HECT-type E3 ubiquitin ligase in Tregs, plays a specific role in restraining Th2 cell responses. This finding has important implications for understanding the pathogenesis of allergy and asthma.

Introduction

Tregs, which are characterized by the expression of the transcription factor Foxp3, are instrumental in the induction and maintenance of immune tolerance and homeostasis (1, 2); however, the molecular mechanisms underlying Treg-mediated immunoregulatory functions remain elusive. This issue is complex, considering that Tregs are capable of executing their immunosuppressive activity against a broad and diverse array of antigens and within different microenvironments. For example, Tregs can suppress IFN-γ–producing Th1, IL-17–producing Th17, and IL-4–producing Th2 responses. This leads to the question: Do Tregs use universal suppressive mechanisms or do these cells employ environmentally orientated programs of suppression enacted in response to distinct inflammatory cues?

It is generally accepted that Tregs use an arsenal of mechanisms to suppress the immune response through certain surface molecules (e.g., CTLA4, CD25, CD73, CD39) and secretion of immunoregulatory cytokines (e.g., TGF-β, IL-10) (3, 4). These mechanisms explain many, but not all, of the immunosuppressive activities of Tregs. Recent evidence suggests that Tregs suppress different types of T cell–mediated immune responses through the acquisition of specific T effector cell transcriptional programs, depending on the context and the location of inflammation (5). For example, Treg-mediated specific suppression of Th1 cells requires the expression of the transcription factor T-box 21 (TBET). Treg-specific deletion of *Tbet* results in uncontrolled type 1 inflammation (6). In a similar vein, Treg-specific deletion of the gene encoding STAT3 leads to dysregulated Th17 responses (7), implying a key role for STAT3 in Treg control of Th17-mediated inflammation. Intriguingly, Treg-specific knockout of *Irf4*, a transcription factor involved in both Th2 and Th17 cell differentiation, causes the selective dysregulation of autoreactive Th2 responses, suggesting that IRF4 is required for Treg suppression of Th2 cells (8). In this issue of the *JCI*, Jin et al. (9) reveal an indispensable function of Itch, a HECT (homologous to E6-associated protein C terminus) E3 ubiquitin ligase, in Treg-regulated Th2 responses in mice. Targeted deletion of *Itch* in Foxp3$^+$ cells resulted in the uncontrolled production of IL-4, IL-5, and IL-13 by Tregs and, surprisingly, by Itch-sufficient CD4$^+$ effector T cells (9).

Without Itch in Tregs, Th2-type inflammation is uncontrolled

Itch was originally identified in a mutant mouse that displayed skin scratching and abnormal immune disorders (10). *Itch*$^{-/-}$ mice exhibit swollen lymph nodes, enlarged spleens, and increased Th2-type inflammation in the lungs and digestive tract (11). The excess Th2 inflammation in these mice was attributed to the inability of *Itch*$^{-/-}$ CD4$^+$ T cells to differentiate into inducible Tregs (iTregs) (12, 13) in response to TGF-β (14); however, an intrinsic role for *Itch* in thymic-derived Treg cells (tTregs or nTregs) remains unknown.

Jin et al. developed a Treg-specific *Itch* knockout mouse by crossing *Itch*$^{f/f}$ mice with *Foxp3*^{Cre} mice (*Itch*$^{f/f}$*Foxp3*^{Cre}) to investigate the role of Itch in tTregs. Surprisingly, the *Itch*$^{f/f}$*Foxp3*^{Cre} mice appeared normal at birth, but later exhibited lymphoproliferative disorder, pulmonary inflammation, skin lesions, decreased weight, and a higher mortality rate. Since Itch regulates Th2 cytokine production (11), the authors challenged *Itch*$^{f/f}$*Foxp3*^{Cre} mice with OVA in an experimental model of asthma. They found that compared with control mice, *Itch*$^{f/f}$*Foxp3*^{Cre} mice had more severe lung inflammation with dramatic increases in OVA-specific IgE and Th2 cytokines including IL-4, IL-5, and IL-13 in the BAL. These results raised the possibility that aberrant Th2 inflammation was a systemic event in *Itch*$^{f/f}$*Foxp3*^{Cre} mice.

To address the possibility that Th2 inflammation is systemically altered in *Itch*$^{f/f}$*Foxp3*^{Cre} mice, Jin et al. examined animals between 6 and 8 weeks of age, when signs of inflammation first appeared. There were no changes in the thymus, but the number of splenic CD4$^+$ and CD8$^+$ T cells was increased along with activated T cells in *Itch*$^{f/f}$*Foxp3*^{Cre} mice compared with age-matched WT mice. Importantly, ex vivo analysis revealed that CD4$^+$ T cells

Conflict of interest: The author has declared that no conflict of interest exists.

Citation for this article: *J Clin Invest.* 2013; 123(11):4576–4578. doi:10.1172/JCI72477.