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Preventing the Progression of AKI to CKD: The Role of Mitochondria

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AKI concerns up to one half of patients hospitalized in intensive care units and is associated with increased mortality and increased hospital stay independent of comorbidities and severity of the illness.[1] In addition to acute repercussions, one of the most dreaded consequences of AKI, even after apparent recovery, is the associated increased risk of CKD in the long term. This association is also observed for mild forms of AKI. Whether AKI is causal for CKD progression or merely identifies patients at higher risk remains debated, but several strands of experimental evidences show that AKI enhances fibrogenesis and thereby, CKD progression risk.[2]

Despite years of research, no drug has been shown to prevent AKI in patients, whereas numerous therapies have been tested successfully in animal models. This lack of clinical translation has questioned the animal models and preclinical study design of AKI.[3] Targeting AKI prevention is also difficult, because the mechanisms involved in various types of AKI differ, making it unlikely that a unique therapy may prevent all AKI types. In addition, identification of patients at risk of AKI is still difficult, and large patient numbers may be treated unnecessarily. Because decreasing the prevalence of CKD is of uttermost importance, a new paradigm has emerged over the last years, refocusing the attention on the transition from AKI to CKD rather than the prevention of AKI itself.[2] Indeed, if a treatment may be given after the acute insult, the therapeutic window will be larger, and patients will be easier to identify. Because not all patients are at equal risk of CKD development after AKI, better identification of patients at risk will also be needed to avoid unnecessary treatment. Currently, no drug able to halt the AKI to CKD transition is available in humans.

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In this perspective, a very interesting aspect of the study by Szeto *et al.*[4] in this issue of the *Journal of the American Society of Nephrology* is the long (9 months) follow-up after ischemia-reperfusion injury (IRI) in rats. They confirm that AKI is not merely an acute phenomenon but results in long-lasting morphologic and functional consequences. They show that AKI induces an increase in profibrotic and proinflammatory cytokines from 1 to 9 months after an acute injury in rats, leading to progressive increase in glomerulosclerosis and interstitial fibrosis, which are both hallmarks of CKD. They further describe long-lasting signs of endothelial injury as well as damage to capillary loops and podocytes, likely participating in fibrosis and glomerulosclerosis progression. Simultaneously, major alterations of mitochondria, displaying loss of cristae and matrix density, were apparent in endothelial cells, podocytes, and tubular cells by transmission electron microscopy up to 9 months after the injury. Such long follow-up after an ischemic injury has rarely been performed in animal models of AKI and brings crucial information to understanding the AKI to CKD transition. The data presented here are in line with recent data showing that persistence of mitochondrial morphologic alterations and metabolic dysfunctions at 14 days after IRI identify tubuli that will undergo atrophy compared with the ones that will regenerate after an ischemic insult.[5] AKI may thus provoke long-term mitochondrial damage, which perpetuates kidney injury, a pathway that seems relevant for potential interventions.

Are mitochondria thus a promising target to avoid the AKI to CKD transition? Several pathways are probably involved in the progression of acute kidney lesions to the chronic state and seem common to various AKI types, although IRI remains the most studied model in animals. Hypoxia inducible factor activation before the ischemic injury may alleviate resulting fibrosis. Pharmacologic nuclear factor erythroid 2-related factor 2 (NRF2) activation and alterations of tubular cell cycle are being studied.[2] Recently, several groups have reported that energy metabolism and mitochondrial function are altered in various types of AKI, including ischemic and septic ones, and that alterations of key mitochondrial biogenesis regulators drive these acute injuries to become chronic.[5–7] Proximal tubular cells are highly metabolic cells relying only on aerobic metabolism. Fatty acid oxidation by mitochondria is a major energy source, and its alteration is involved in various types of AKI and CKD leading to lipid accumulation, ATP depletion, and fibrosis in proximal tubular cells.[8] Targeting mitochondria by restoring their metabolism, redox state, and dynamics and enhancing biogenesis all seem promising in preclinical studies in AKI.[9] Other than altering metabolism and thereby, tubular cell function, mitochondrial dysfunction has also been reported to induce the inflammasome directly.[10] Blocking the proinflammatory reaction seems promising, and a recent study showed that integrin CD11b/CD18 blockade ameliorated fibrosis post-AKI in primates subjected to IRI and

unilateral urinary obstruction.[11] Because mitochondria seem to play a primary role in AKI and may induce the inflammasome, it made sense to target mitochondria first and determine a potential beneficial effect on inflammation. Szeto-Schiller (SS) peptides are among novel mitoprotective drugs being tested in the field of experimental AKI. SS peptides are synthetic peptides with mitoprotective properties.[12] These peptides selectively bind cardiolipin in the mitochondrial inner membrane and protect mitochondrial cristae. Cardiolipin also allows better function of the respiratory chain complexes. Structural studies suggest that the complexes between SS-31 and cardiolipin prevent peroxidase activity and improve mitochondrial respiration and ATP production. Altogether, SS-31 seems to restore mitochondrial structure and function and decrease reactive oxygen species production by mitochondria. In their study, Szeto *et al.*[4] report the presence of inflammasome activation in conjunction with mitochondrial dysfunction late after an ischemic injury. Inflammatory activation was largely improved by restoring mitochondrial function by SS-31, pointing to mitochondrial dysfunction as causal in inflammasome stimulation post-AKI. This observation points to a central role of mitochondria in the proinflammatory and profibrotic response observed in the post-AKI chronic state.

SS-31 has been used experimentally in the field of cardiovascular disease and shown to significantly decrease myocardial infarct size and improve heart failure. Several phase 1 and 2 clinical trials are ongoing in cardiovascular and muscle pathologies. SS-31 has been also shown to be beneficial in different types of experimental kidney disease. In IRI, SS-31 administered before the injury ameliorated renal function, decreased tubular injury, and improved tubular cells regeneration.[13] In CKD models, SS-31 decreased glomerular and tubular lesions induced by a high-fat diet and diabetes and decreased injury related to aging and urinary tract obstruction.[14–16] In larger animals, SS-31 was shown to decrease renal microvascular and fibrotic lesions resulting from atherosclerotic renovascular lesions in pigs.[17] Results of a human trial are awaited. All of these observations imply that mitochondrial dysfunction underlies the pathogenesis of several acute kidney diseases and CKDs. This study shows for the first time the beneficial effect of SS-31 not only in AKI prevention but also, on the long-term renal consequences of AKI when administered long enough after the injury and for a limited period of time. Indeed, the peptide was administered 1 month after ischemia-reperfusion for 6 weeks in rats, with apparent complete recovery of renal function. This treatment avoided the development of interstitial fibrosis and glomerulosclerosis, reversed mitochondrial damage in podocytes and tubular cells, improved vessel recovery, and decreased the synthesis of TGF-β, IL-1β, and IL-18 observed until 9 months after the acute injury. The effect of SS-31 on metabolic pathways, such as free fatty acid oxidation, was not described. Although data on renal function and proteinuria would have reinforced the observation, renal structural differences between groups are quite evident.

This observation is of major relevance for a potential clinical translation. Indeed, the long follow-up of the study shows that mitochondrial lesions are persistent after AKI, inducing fibrosis even in the case of apparent renal function recovery long after the acute injury. The data suggest that mitochondrial dysfunction is central to the AKI to CKD transition, because targeting mitochondria reverses the proinflammatory and profibrotic phenotype, which is observed in the long-term evolution. Finally, conceptually, the use of a treatment 1 month after the injury and for a limited period of time opens a new window of opportunity for therapeutic intervention if applicable in humans. This suggests that we may have the time to identify patients with persisting mitochondrial dysfunction after an AKI and that we may reverse it pharmacologically, notably with SS peptides. Although the observation is still experimental and needs confirmation in other types of AKI, notably septic AKI (the most frequent form in patients), as well as on renal function parameters, such as GFR and proteinuria, it enlightens new concepts of treatment for AKI to prevent the dreaded progression to CKD. Whether this observation will directly translate into clinical treatment is not certain, because many promising compounds have failed the animal to human transition in the field of AKI. Nevertheless, Szeto *et al.*[4] confirm that we may have to change our approach on AKI treatment, focusing more on the post-AKI phase, where the therapeutic window is larger and the population is more identifiable.

DISCLOSURES

None.

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See related article, "Mitochondria Protection after Acute Ischemia Prevents Prolonged Upregulation of IL-1β and IL-18 and Arrests CKD," on pages 1437–1449.

The Use of Sildenafil for Glomerular Disease

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Transient receptor potential channel 6 (TRPC6) is a Ca^{2+} ion transport channel associated with the slit diaphragm of podocytes, and is indispensable for regulation of structural components of podocytes and renal function.[1] Since the discovery of a TRPC6 gain-of-function mutation that causes familial FSGS, TRPC6 activation has been associated with several progressive glomerular diseases.[2,3] In fact, TRPC6 in the context of kidney disease has become quite ubiquitous, and its activity is being considered by many as an indicator of podocyte vulnerability and progressive kidney disease.[4] It is of no surprise that researchers began investigating blocking TRPC6 activity, thereby reducing deleterious Ca^{2+} influx in an effort to adjust the podocyte cytoskeleton. In the current issue of the *Journal of the American Society of Nephrology*, Sonneveld *et al.*[5] found sildenafil (*i.e.*, Viagra) has antiproteinuric effects *via* a mechanism involving peroxisome proliferator-activated receptor γ (PPAR-γ) in mouse podocytes, and may be an effective regulator of TRPC6 signaling for use in treating glomerular disease.

As a successful erectile dysfunction drug, sildenafil occupies the active site of phosphodiesterase type 5 (PDE5), giving rise to cGMP, which initiates smooth muscle relaxation and increased blood flow. Although sildenafil is a well known PDE5 blocker in penile and cardiac tissue, its role in podocytes is poorly defined. Sonneveld *et al.* contribute to ongoing research efforts that have demonstrated the renoprotective effects of sildenafil by more clearly defining a pathway in which sildenafil blocks PDE5 leading to cGMP accumulation, protein kinase G-1 (PKG-1) activation, and in turn, PPAR-γ activation to downregulate TRPC6 expression.[5] In podocytes, cGMP accumulation is known to suppress renal disease,[6] and podocyte responsiveness to PDE5 blockers has opened the door to cGMP regulation as a means of treating podocyte injury. Several groups have extensively studied components of pathways activated by cGMP accumulation in podocytes, and a great deal of evidence supports TRPC6 inactivation as a mechanism to treat kidney disease. For example, cGMP accumulation has been linked to podocyte contractility, mobility, and cytoskeletal structure[7]; PKG-1 is associated with poor clinical outcome in renal cell carcinoma[8]; PPAR-γ agonists have been shown to protect podocytes from nephropathies[9]; and overexpression of TRPC6 alone is sufficient to cause podocyte damage and subsequent glomerulopathies.[10,11] Collectively, these findings highlight the importance of crosstalk among cGMP, PKG-1, PPAR-γ, and TRPC6, and demonstrate the importance of TRPC6 signaling in kidney disease.

Sonneveld *et al.* found PDE5 is expressed in podocytes, and sildenafil can have antiproteinuric effects through PPAR-γ to decrease TRPC6 expression levels, and ultimately minimize deleterious Ca^{2+} influx.[5] Transcriptional downregulation of TRPC6 *via* PPAR-γ in response to sildenafil ameliorated podocyte injury, and was deemed more important than affecting TRPC6 channel functionality directly, as previously reported.[12] cGMP accumulation had no effect on Ca^{2+} influx in the presence of PPAR-γ antagonists, suggesting PKG-1–mediated binding of PPAR-γ to the TRPC6 promoter is the pivotal interaction regulating Ca^{2+} homeostasis. In the context of clinically approved drugs, this study is a reminder of the potential benefits of repurposing approved drugs. After all, sildenafil was not intended as an erectile dysfunction drug and is, in essence, a side effect drug itself. Complex pathways with

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