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EDITORIAL COMMENT

Mitochondrial DNA in Uremia and New Targets to Treat Myocardial Hypertrophy in the Cardiorenal Syndrome*

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The scientific literature has seen an explosion of work on the interconnection between heart and renal disease, with cardiac dysfunction caused by chronic kidney disease (CKD) known as cardiorenal syndrome type IV. The decrease in renal clearance of salt and water and volume overload are frequently seen as the culprit and target for treating. But exciting work on the effects of the CKD milieu on mitochondrial function suggests that uremic toxins, as well as excess fluid, may be a trigger and that another option for treatment lies in interfering with mitochondrial dysfunction rather than just increasing the dose of loop diuretic agents or adding more angiotensin-converting enzyme (ACE) inhibitor.

In this issue of *JACC: Basic to Translational Science*, Han et al[1] set out to show that mitochondrial damage occurs early in CKD and sets up a chain of events leading to cardiac myocyte hypertrophy. The "uremic milieu" leads to mitochondrial damage through increased release of reactive oxygen species, release of mitochondrial DNA (mtDNA) and eventual up-regulation of nuclear factor (NF)-κB. NF-κB activates ornithine carboxylase (OCD) metabolism to putrescine with buildup in cardiac myocytes. mtDNA is sensed by the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway, an early mechanism for regulating response to microbial and oncologic threats.[2] This in turn leads to increased activation of genes involved in cardiac hypertrophy. Han et al[1] showed in a 5/6 nephrectomy model of CKD in mice that administration of VBIT-4 interfered with mitochondrial outer membrane permeabilization (MOMP), activation of NF-κB and up-regulation of the cardiac myocyte hypertrophy program. Further inhibiting STING with the compound C-176 also alleviated cardiac myocyte hypertrophy as demonstrated echocardiographically and histologically. They confirmed the results with small interfering RNA and STING knock-out mice.

One of the limitations of the study is that the authors do not describe specific elements of the uremic milieu that lead to mitochondrial damage by increasing reactive oxygen species. Of the more than 130 substances considered to be uremic toxins, 30 appear closely related to mitochondria. One among those frequently mentioned and relevant to this article is putrescine. Not only do uremic toxins affect mitochondria, but mitochondria may be the source of some uremic toxins or fail to break others down.

Others have looked at "maintaining mitochondrial homeostasis"[3] as a way to interrupt the vicious cycle of heart failure and acute kidney injury/CKD. Abnormal mitophagy in which damaged mitochondria are degraded may lead to increased renal tubular epithelial cell death through depletion of ATP stores and increased accumulation of reactive oxygen species in cardiac myocytes. In their review, Shi et al[3] suggest that mitotherapy is a potential strategy for treating heart failure and call for increased research into therapies to prevent mitochondrial damage.

Disruptions in ATP synthesis by the shift to pyruvate metabolism from the preferred metabolism of

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glucose from fatty acetyl CoA metabolism leads to disruption of oxidative phosphorylation and ATP generation.[3] That disruption leads to increased mitochondrial outer membrane permeabilization caused by activation by oxidative damage of the voltage-dependent anion channel 1 (VDAC1) and release of mtDNA, sensed by gCAS, which activates STING and ultimately NF-κB.

A critical part of the chain of events is the alternative non-ATP-producing pathway of polyamine metabolism, which the authors point out as essential for cell growth, particularly the polyamine precursor putrescine. NF-κB up-regulates OCD conversion of polyamines to putrescine.

Kim et al[1] demonstrate that the initial effect of the CKD milieu is on gene transcription: RNA sequencing showed down-regulation of genes related to muscle contraction and up-regulation of genes related to ventricular hypertrophy. They further noted down-regulation of mitochondrial genes in the myocardia of CKD mice as well as mitochondrial swelling and vacuolization. Investigation of the role of cGAS and STING in activating NF-κB used specific STING-knockout mice to demonstrate the lack of cardiac hypertrophy in those mice by preventing activation of NF-κB. This further blunted up-regulation of ODC and buildup of putrescine in mouse cardiac myocytes. The authors suggest that NF-κB acts at the transcriptional level on the OCD promotor.

To demonstrate the therapeutic potential of intervening at the mitochondrial level, the investigators used pharmacologic agents VBIT-4, which inhibited VDAC1 dimerization, which is necessary for increased MOMP; pyrrolidine dithiocarbamate ammonium (PDTC), a specific inhibitor of NFkB; DMFO, an irreversible inhibitor of ODC; and C-176, a specific STING inhibitor that reduced the accumulation of polyamines in cardiac myocytes. VBIT-4 has been used in other cardiac models to block VDAC1. Klapper-Goldstein et al[4] used VBIT-4 to block VDAC1 in rats and prevent atrial fibrosis and mitochondrial dysfunction after exposure to excessive levels of aldosterone. They wrote that the exact mechanism is not clear. Others have looked at the positive effects of blocking VDAC1 with VBIT-4 on mitochondrial dysfunction in a mouse model of inflammatory bowel disease.[5] PDTC is widely used as a specific inhibitor of NF-κB in other cardiac studies of fibrosis, and the authors note that PDTC derivatives have been put to therapeutic use, as have derivatives of DFMO.

Targeting the cGAS-STING pathway has become an attractive option in cardiovascular and metabolic disease.[2] Human and mouse STING share about 70% homology in terms of amino acid makeup, suggesting the utility of the mouse model. Moreover, the pathway operates across other pathologies, such as acute myocardial infarction, diabetic cardiomyopathy, obesity, vascular disease, nonalcoholic fatty liver, and steatohepatitis. Human trials of small-molecule STING inhibitors are underway in oncology. C-176, the STING inhibitor, has been used in a diabetic cardiomyopathy model to block inflammation and apoptosis.[6] Overall, the mouse model and small interfering RNA experiments help demonstrate the potential therapeutic benefits of the pharmacologic interventions at several key points along the pathway.

Although the pathways in this paper have been studied individually, the value of the experiments comes from describing the interconnected causal relationships of each step and the downstream effects of individual intervention to prevent release of mtDNA, block activation of cGAS-STING and NF-κB, and block activation of OCD and buildup of putrescine. The in vitro cellular experiments further demonstrate that the pathways lead to myocyte hypertrophy without the in vivo effects of volume overload in CKD or hypertension in the mouse 5/6 nephrectomy model.

None of this is to say that there will no longer be a role for loop diuretic agents to reduce volume overload in the cardiorenal syndrome or for ACE inhibitors to prevent cardiac remodeling by reducing afterload and blocking aldosterone. Rather, the work by Han et al[1] suggests a much more nuanced appreciation of the effects of the uremic milieu on cardiac function and points to new pathways for treating myocardial hypertrophy in the cardiorenal syndrome.

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