
See related article, "LMX1B Mutations Cause Hereditary FSGS without Extrarenal Involvement," on pages 1216–1222.

Maintaining Mitochondrial Morphology in AKI: Looks Matter
Andrew M. Hall
Institute of Anatomy, University of Zurich, Zurich, Switzerland

Mitochondrial morphology and function are inextricably linked. The classic textbook view of mitochondria as inert objects simply producing ATP for their host cells does them a disservice; they are highly complex and dynamic intracellular organelles, capable of moving, fusing, and dividing, to exchange genetic information and maintain their integrity.1 The characteristic double-membrane structure of mitochondria, with a cylindrical outer membrane surrounding an inner membrane (IMM) folded to form invaginating cristae, exists for important ergonomic reasons. The extensive folding of the IMM increases the total surface area in which oxidative phosphorylation (OXPHOS) can take place, whereas the tight ridges of the cristae provide enclosed regions where protons pumped by OXPHOS complexes can be concentrated into gradients to optimally drive ATP synthesis.2 The localization of OXPHOS complexes along the cristae is distinctive and ordered, and normal complex function is required to maintain the architecture of the IMM.3

Ischemia induces structural changes in mitochondria, typically swelling and disappearance of the IMM cristae, due to ATP depletion and loss of osmotic regulation.4 Given that mitochondrial structure and function are closely linked, it follows that interventions to preserve the former might also improve the latter during an ischemic insult. A major component of the IMM is cardiolipin (CL), a phospholipid originally discovered in the heart. CL has a key role in maintaining the normal architecture of the IMM and anchoring OXPHOS complexes in locations for optimal function, and deficiency of CL synthesis causes severe multisystem disease associated with mitochondrial abnormalities (Barth syndrome5). During ischemia, reactive oxygen species (ROS) cause peroxidation of CL, and this process is enhanced by peroxidase activity of cytochrome c (a cationic component of the OXPHOS chain that is normally closely associated with anionic CL) in the presence of H2O2; this causes an alteration in the structure of cristae, leading to a defect in the functional capacity of mitochondria to produce ATP. Dissociation of cytochrome c from CL can lead to its release into the cell, activation of programmed cell death pathways, and irreversible opening of the mitochondrial permeability transition pore (which, intriguingly, may be formed of dimers of ATP synthase, according to very recent research6).

The renal proximal tubule (PT) is particularly vulnerable to hypoxia, because it is dependent on aerobic metabolism to generate ATP, and ischemia-reperfusion injury (IRI) is a major cause of AKI. IRI induces rapid swelling and fragmentation of mitochondria in the PT,8 leading to sustained energetic deficits9 and activation of cell death pathways.10 Increased mitochondrial ROS production is thought to be a major mechanism in the pathogenesis of IRI, particularly during reperfusion when O2 is represented to damaged OXPHOS complexes.11 Nonspecific antioxidants have proven disappointing as a therapy in AKI, perhaps partly because of the realization that nonmitochondrial ROS have important physiologic signaling roles in the kidney.12 There has therefore been great interest in the development of antioxidants specifically targeted to the mitochondria; two such agents, mito Q and SkQ1, selectively accumulate in the mitochondrial matrix on account of their positive charge and have shown renoprotective effects in models of cold storage injury13 and IRI,14 respectively.

An alternative class of mitochondrial targeted agents are the Szeto-Schiller (SS) peptides; although they are also positively charged, their mechanism of uptake seems to be independent of mitochondrial membrane potential (perhaps increasing their usefulness under ischemic conditions when mitochondria may be de-energized), and they accumulate predominantly in the IMM.15 Previous studies have suggested that one such peptide, SS-31, protects cells against induced oxidative stress in vitro16 and reduces infarct size in cardiac IRI.17 More recently, it was demonstrated that SS-31 has profound protective effects during IRI in the kidney, including better preservation of mitochondrial structure and function in PT cells, and reduction in levels of oxidative stress; these effects were associated with improvements in histology, and amelioration of changes in serum creatinine, BUN, and fractional excretion of sodium.18

Although SS-31 is thought to have antioxidant properties, the exact mechanisms underlying its protective actions in IRI in

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Andrew M. Hall, Institute of Anatomy, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland. Email: andrew.hall@uzh.ch

Copyright © 2013 by the American Society of Nephrology
the kidney remained unclear. Now, in an interesting follow-up study published in this issue of JASN, Birk et al. provide new evidence that the effects of SS-31 are mediated, at least in part, via interaction with CL and inhibition of cytochrome c–mediated peroxidation. First, using a fluorescent amino acid incorporated into the protein, they demonstrated that SS-31 interacts with anionic phospholipids, and that the effect was greatest with CL. Next, they confirmed in vitro that cytochrome c can act as a peroxidase in the presence of H₂O₂ and CL, and that this process is inhibited by SS-31. Moving in vivo, they then demonstrated in rats exposed to 30 minutes of renal ischemia that SS-31 reduced mitochondrial swelling and better maintained the architecture of cristae in PTs compared with saline-treated animals. Furthermore, upon reperfusion, SS-31–treated mitochondria rapidly reverted to their normal elongated shape within minutes, in contrast to untreated animals where structural abnormalities persisted.

De-energization of mitochondria in the PT is associated with rapid degeneration of the apical membrane brush border transport apparatus, which normally requires ATP to maintain its complex actin cytoskeleton. This process is accompanied by redistribution of adhesion molecules from the basolateral membranes to the cytosol, leading to cell shedding, obstruction of tubular flow, and back-leak of solutes, all of which then contribute to a fall in GFR. In parallel with its effects on mitochondrial integrity, SS-31 also better preserved the structure of the brush border and the basolateral localization of adhesion molecules in PT cells after IRI, and reduced the number of apoptotic tubular cells in the outer medulla.

Taken together, these results support the novel and plausible hypothesis that, in addition to its antioxidant properties, the protective effects of SS-31 during IRI are due to interaction with CL in the IMM and inhibition of cytochrome c peroxidase activity, leading to reduced peroxidation of CL. Further direct evidence will be required to prove that this process occurs in vivo, and other studies have suggested that mitochondrial antioxidants that are not specifically targeted to the IMM are also protective in IRI. But whatever the underlying mechanism, it seems clear that SS-31 can ameliorate adverse changes in mitochondrial structure and function in ischemic AKI, with the result that tubular cell structure and overall kidney function are better preserved. On the basis of these promising findings, the drug is now undergoing clinical trials in humans. Will it be more successful than its many predecessors in the AKI field? For the sake of patients, the answer will hopefully be yes, but some notes of caution should be heeded.

First, although mitochondrial ROS are widely implicated in the pathogenesis of IRI, it cannot be overstated that our understanding of mitochondrial biology in vivo is limited and is based mostly on extrapolation from in vitro experiments performed on isolated cells and organelles. We simply just do not know how much ROS are actually generated by mitochondria in living mammals, and there is an urgent need to develop and embrace new technologies that will enable us to measure this. Conceivably, rates of production could be significantly lower than under in vitro conditions, due to lower oxygen tension and substrate availability, and differences in redox state resulting from higher rates of ATP synthesis. Second, as has been alluded to already, ROS have important signaling roles, and mitochondrial generated ROS might be important in the activation of hypoxia defenses during ischemia, such as the hypoxia-inducible factor system. Third, a recent detailed study of IRI in human kidneys highlighted significant differences from animal models, including, crucially, much less severe structural damage in PT cells, and rapid resolution of mitochondrial swelling after reperfusion in the absence of any therapeutic intervention. Fourth, IRI-induced apoptosis occurs mainly in the distal tubule, so it is difficult to relate the reduction in the number of apoptotic cells in SS-31–treated kidneys to the mitochondrial effects of the drug in the PT. Lastly, as has been noted before, SS-31 was given before the onset of ischemia in experiments, which means that its beneficial effects in clinical practice may be limited to scenarios where ischemic AKI is predictable, such as transplantation.

One final lesson might be learned from the story of SS peptides. As the developers openly admit, their discovery that this class of compounds are potent modulators of mitochondrial function occurred completely by accident, while they were working in a very different field. SS peptides can thus now be added to the long list of useful drugs stumbled on by serendipity, which already includes penicillin, lithium, cisplatin, sildenafil, and many others—without which modern medicine would be much the poorer. Meanwhile, the recent wide-scale adoption of targeted approaches and high-throughput screening has not produced the anticipated increase in novel drug development. History tells us that medical science can move forward in rapid and unexpected directions; food for thought for advocates of exhaustive grant review processes and designers of shiny new translational research centers. Looks matter, for sure, but what patients really want are new drugs that work, however they are discovered.

ACKNOWLEDGMENTS

A.M.H. is supported by the Swiss National Centre of Competence in Research (NCCR) Kidney Control of Homeostasis.

DISCLOSURES

None.

REFERENCES

Vascular Access for Hemodialysis in Older Adults: A “Patient First” Approach

Ann M. O’Hare
Veterans Affairs Puget Sound Healthcare System, University of Washington, Seattle, Washington

In their landmark 1996 paper in JAMA, Hirth and colleagues reported that most patients in the United States with permanent vascular access were undergoing dialysis via a prosthetic graft rather than an autogenous fistula, despite known higher rates of infection and thrombosis associated with grafts. These authors also reported large regional differences in rates of graft use—ranging from 23% of patients with a permanent access in New England to 85% in the East South Central census region—that were not explained by variation in patient characteristics.

These observations served as a wake-up call to the renal community, which responded with a series of initiatives to increase fistula use. In 1997, the Kidney Disease Outcomes Quality Initiative (KDOQI) published clinical practice guidelines for hemodialysis vascular access that strongly favored the use of fistulas over grafts. In 1998, the Health Care Financing Administration (now Centers for Medicare and Medicaid Services [CMS]) developed clinical performance measures for vascular access that included target fistula and catherer use of a ratiometric mass spectrometry probe targeted to the mitochondrial matrix. Cell Metab 13: 340–350, 2011


