Mitochondrial Thioredoxin
Novel Regulator for NADPH Oxidase and Angiotensin II–Induced Hypertension

Tohru Fukai

The source of reactive oxygen species (ROS) produced in cardiovascular systems includes NADPH oxidase, xanthine oxidase, and uncoupling of endothelial NO synthase (eNOS) as well as mitochondria. In particular, NADPH oxidase has been considered a predominant source of ROS in the pathogenesis of hypertension, atherosclerosis, cardiac hypertrophy, and heart failure. Recent data suggest that angiotensin (Ang) II, a potent hypertensive hormone which is known to activate NADPH oxidase, induces mitochondrial dysfunction, which, in turn, promotes excess amounts of ROS, eg, superoxide (O$_{2}$$^{-}$), hydrogen peroxide (H$_{2}$O$_{2}$), and peroxynitrite from mitochondria. This contributes to endothelial dysfunction by reducing NO bioavailability and activating apoptotic signaling, thereby progressing cardiovascular disease, neurodegenerative disease, and aging. The role of mitochondrial ROS is demonstrated by previous reports that transgenic mice overexpressing catalase targeted to the mitochondria exhibit an extended life span. Mice overexpressing peroxiredoxin 3, the mitochondria-specific peroxidase linked to thioredoxin 2 (Trx2), show improved survival after myocardial infarction. Furthermore, Ang II–converting enzyme inhibitors and Ang II type I receptor blockers prevent age-related mitochondrial dysfunction, hypertension-induced renal mitochondrial dysfunction, and cardiac mitochondrial dysfunction in the setting of acute ischemia. However, the role of mitochondria-derived ROS and its relationship with NADPH oxidase–derived ROS in Ang II–induced hypertension remain unclear.

One of the major antioxidant defense systems against mitochondrial ROS (in particular, H$_{2}$O$_{2}$) is thiol-reducing systems, including thioredoxin (Trx), glutaredoxin, and the glutathione system. The Trx system (Trx, Trx reductase, and NADPH) reduces oxidized cysteine groups on protein through an interaction with the redox-active center of Trx (Cys-Gly-Pro-Cys) to form a disulfide bond, which, in turn, can be reduced by Trx reductase and NADPH. In mammals there are ≥3 different thioredoxins: (1) Trx1 is present in the cytosol but can also translocate to the nucleus; (2) Trx2 has a consensus signal for translocation to the mitochondria; and (3) SP-Trx is found in spermatozoa. Mitochondrial Trx systems (Trx2, TrxR2, and Prx3) are critical in protecting cells from mitochondria-dependent ROS and apoptosis. Little is known about the functional roles of Trx2 in hypertension.

In this issue of Hypertension, using transgenic mice overexpressing Trx2 (hTrx2-Tg), Widder et al provide the novel evidence that mitochondrial antioxidant Trx2 plays a critical role in regulating endothelial function and systolic blood pressure in Ang II–induced hypertension. Overexpression of Trx2 decreases “total” as well as “mitochondrial” ROS in aortas from mice infused with Ang II, suggesting that mitochondrial ROS play a critical role in regulating Ang II–induced hypertension. A cross-talk between NADPH oxidase- and mitochondria-derived ROS appears to exist in Ang II–induced mitochondrial dysfunction, ROS production, and preconditioning and nitroglycerin-triggered vascular dysfunction. Ang II activates NADPH oxidase, thereby elevating cytosolic ROS (in particular, O$_{2}$$^{-}$), which triggers mitochondrial ROS elevation. This mechanism seems to be mediated through either activation of the mitochondrial ATP-sensitive potassium channel or mitochondrial dysfunction induced by peroxynitrite produced by the reaction of O$_{2}$$^{-}$ with NO. This mitochondrial ROS further increases ROS by inducing the mitochondrial permeability transition (ROS-triggered ROS formation). In this study, uncoupling eNOS may not be a source for Ang II–induced O$_{2}$$^{-}$ production, because aortic tetrahydrobiopterin levels and the eNOS dimer:monomer ratio are not changed after chronic Ang II infusion. Widder et al have found that chronic Ang II infusion increases expression of the NADPH oxidase subunits Nox2, p22(phox), p47(phox), and Rac-1 in wild-type mice, which is attenuated in mice overexpressing Trx2. These results suggest that mitochondrial ROS increase expression of NADPH oxidase components. Given that NADPH oxidase can be stimulated by H$_{2}$O$_{2}$ and lipid peroxides, the mitochondrial ROS, including H$_{2}$O$_{2}$, might stimulate NADPH oxidase activity and expression in a feed-forward fashion. Thus, the decrease in NADPH oxidase expression and total ROS production in Ang II–infused hTrx2-Tg mice might be caused by inhibition of cross-talk between mitochondrial- and NADPH oxidase–derived ROS (Figure).

The hTrx2-Tg mice improve endothelial dysfunction induced by Ang II infusion, suggesting that mitochondrial ROS inhibit endothelial cell function, as reported previously. This protective effect of Trx2 is not attributable to an increase in vascular eNOS levels, because chronic Ang II infusion did not alter vascular eNOS levels in both wild-type and hTrx2-Tg mice. Because mitochondrial ROS may stimulate NADPH oxidase, overexpression of Trx2 may block ROS production derived from both mitochondria and NADPH oxidase, thereby efficiently preserving NO bioavailability. The hTrx2-Tg mice also prevent vasoconstriction induced by chronic Ang II infusion, indicating that mitochondrial ROS contribute to Ang II–mediated vasoconstriction.

Zhang et al reported that transgenic mice overexpressing “endo-

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association. From the Section of Cardiology, Department of Medicine, and Department of Pharmacology, University of Illinois at Chicago. Correspondence to Tohru Fukai, Departments of Medicine (Section of Cardiology) and Pharmacology, Center for Cardiovascular Research, University of Illinois at Chicago, 835 S Wolcott, MC/868, E403MSB, Chicago, IL 60612. E-mail: tfukai@uic.edu

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Fukai

The data presented by Widder et al strongly support a critical role for Trx2, as a regulator of mitochondrial ROS, in Ang II–induced hypertension and cardiac hypertrophy (Figure). Moreover, their finding underscores the importance of targeting antioxidant molecules to mitochondria as a new therapeutic strategy to restore vascular function and reduce the pathophysiology of hypertension. This may explain the failure of antioxidants as therapeutic agents in a series of clinical trials and emphasizes the relevance of the manipulation of ROS at the subcellular level.

There are many unanswered questions. What is the role of endogenous Trx2 in vascular function and hypertension? Because Trx2−/− mice are embryonically lethal, study using Trx2−/− mice will provide new information regarding the functional significance of Trx2 in Ang II–induced hypertension and other cardiovascular diseases. Can overexpression of other mitochondrial thiol–reducing systems, eg, glutathione peroxidase, mimic the effect of Trx2? Can overexpression of Trx2 affect other signaling pathways involved in hypertension, eg, deoxyxycorticosterone acetate salt hypertension? Addressing these questions will be essential to understand the mechanism of oxidative stress–dependent cardiovascular diseases and aging in which mitochondrial ROS play an essential role.

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None.

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Tohru Fukai

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