Mitochondria play a major role in oxidative energy production, reduction–oxidation reaction (redox) control and calcium homeostasis. Although mitochondria contain DNA with mitochondrial-specific genes, most mitochondrial proteins are encoded by the nDNA, synthesized in the cytosol, and imported into mitochondria. The expression of nuclear genes that encode mitochondrial proteins that function in metabolic pathways such as the trichloroacetic acid cycle (TCA), oxidative phosphorylation, heme synthesis, and in mitochondrial DNA replication and transcription (e.g., mitochondrial transcription factor A [Tfam]), is coordinately regulated by the transcriptional coactivators PPARγ coactivator (PGC)-1α and PGC-1β through activation of nuclear respiratory factor (NRF)-1 and NRF-2.1

In their recent publications, Plantadosi et al provided insight into the mechanisms underlying the interaction between mitochondria-derived reactive oxygen species (ROS) signaling and mitochondrial biogenesis. First, lipid hydroperoxide regulates Tfam expression through phosphorylation of NRF-1 via Akt activation, which promotes nuclear translocation of NRF-1 and binding to the Tfam promoter.2 Second, carbon monoxide (CO) induced mitochondrial biogenesis via activation of Akt1/PKB and guanylate cyclase, which augmented gene and protein expression of NRF-1 and NRF-2, PGC-1α, and TFAM.3 CO-induced mitochondrial ROS result in the activation of AKT. Third, the antracycline anticancer agent doxorubicin suppresses the nuclear program for mitochondrial biogenesis, and its associated intrinsic antiapoptosis proteins, leading to severe mitochondrial DNA (mtDNA) depletion and apoptosis. CO inhalation or heme oxygenase (Hmo)1 overexpression prevented doxorubicin-induced mtDNA depletion and apoptosis via activation of AKT and guanylate cyclase.4 Lastly, new work in this issue of Circulation Research5 sheds light on the role of NF-E2–related factor (Nrf)2 as a key transcriptional regulator in mitochondrial ROS-dependent induction of NRF-1 mRNA.

There is increasing evidence to suggest that ROS may be a double-edged sword: although they can be toxic to cells, they may also play an important role in cell signaling involved in the antioxidant defense network. ROS are generated from many sources including the Nox family of NADPH oxidases, xanthine oxidase, and mitochondria, where ROS are produced as a byproduct of oxidative energy production. ROS are very unstable and cannot penetrate lipid membranes; they are therefore retained within the compartment in which they are produced. However, ROS can attack neighboring polyunsaturated fatty acids of the membrane and trigger a chain reaction of lipid peroxidation, resulting in the generation of lipid hydroperoxides and α, β-unsaturated aldehydes, such as 4-hydroxy-2-nonenal (4-HNE) (Figure). They are highly electrophilic and react with biomolecules, such as proteins and nucleic acids, generating various adducts. By virtue of their increased chemical stability, these lipid peroxidation products can diffuse greater distances compared with their precursor ROS and can propagate and amplify oxidative injury. Thus, lipid peroxidation products have been implicated in the development and progression of a variety of pathological events such as oxidation of LDL, atherosclerosis, ischemia/reperfusion injury, Alzheimer’s disease, cancers, and cell senescence.

However cells are able to sense macromolecular damage and counteract stress-induced damage to reestablish homeostasis. Electrophilic lipid peroxidation products can trigger a cascade of stress resistant pathways in both a tissue- and cell type–specific manner. The induction of stress-protective mechanisms by stress is referred to as “stress-response hormesis.”6 The principle of stress-response hormesis can be seen in many contexts. For example, the ninja, a group of spies and assassins in feudal Japan, were known to regularly take sublethal doses of poison to build their capacity to detoxify xenobiotics and thus protect themselves against assassination with poison. In cell culture, 4-HNE kills cells at a high dose, whereas pretreatment of cells with low-dose 4-HNE upregulates endogenous antioxidant and phase II enzymes, conferring greater tolerance against subsequent oxidative insult.7 An effect of stress-response hormesis may also be seen in clinical studies that have tested antioxidant supplements for prevention of cardiovascular events8 and cancers9 based on the principle that they should prevent oxidative stress-induced macromolecular damage. In both clinical studies, antioxidant supplements may have failed to identify a beneficial effect because this inevitably attenuates the cell-signaling pathways necessary for protection against oxidative stress and reestablishment of redox homeostasis.6 Following the induction of oxidative stress, 2 basic leucine zipper transcription factors, Nrf2 and activating transcription factor (ATF)-4, are activated at the posttranscriptional level and induce the expression of genes encoding proteins that function as antioxidants and enzymes involved in phase II detoxification and glutathione biosynthesis. Under nonstressed conditions, Nrf2 is tethered in the cytoplasm by Keap1. This complex directs Nrf2 polyubiquitination and degradation. On oxidative stress, Nrf2 is liberated from

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Regenerative Medicine and Advanced Cardiac Therapeutics, Keio University School of Medicine, Tokyo, Japan.

Correspondence to Motoaki Sano, Department of Regenerative Medicine and Advanced Cardiac Therapeutics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582. E-mail msano@sc.itc.keio.ac.jp

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Editorials

Activation of Mitochondrial Biogenesis by Hormesis

Motoaki Sano, Keiichi Fukuda
Keap1 and enters the nucleus, where it can form a heterodimer with the small Maf transcription factor Nrf2 to stimulate the expression of antioxidant response element–containing genes, including NAD(P)H:quinone oxidoreductase, heme-oxygenase 1, γ-glutamylcysteine synthetase, glutathione S-transferase, glutathione peroxidase, glutathione reductase, cysteine glutamate transporter, and multidrug resistance–associated protein 1. Oxidative stress leads to the phosphorylation of the α subunit of translation initiation factor 2 (eIF2α). Phosphorylation of eIF2α inhibits general protein synthesis but specifically upregulates translation of ATF4. ATF4 forms homodimers and heterodimers with members of the AP-1 and C/EBP family of proteins to regulate the expression of genes involved in amino acid metabolism which provide the precursor amino acids necessary for glutathione biosynthesis, such as phosphoserine amino transferase, phosphoserine phosphatase, cystathionine γ-lysate, and methylenetetrafolate dehydrogenase. Thus, Nrf2 and ATF4 coordinately regulate glutathione biosynthesis and the glutathione redox cycle. Intense muscular contractile activity by exercise results in oxidative stress, as indicated by altered muscle and blood glutathione concentrations and increases in protein, DNA, and lipid peroxidation. Interestingly, it was recently reported that excess vitamin C supplements decrease training efficiency via the reduction of the exercise-induced expression of PGC-1α, Nrf2, and Tfam. This observation further suggests that ROS cannot only be considered to be toxic byproducts; they also play an important role in the cell signaling that regulates expression of genes involved in mitochondrial biogenesis. Piantadosi et al first demonstrated a role for Nrf2 in ROS-mediated induction of NRF-1. The NRF-1 promoter contains multiple antioxidant response element motifs and mitochondrial-derived ROS enhance Nrf2 binding to the NRF-1 promoter via AKT-mediated derepression of Nrf2 nuclear translocation. In the heart, however, the role of Nrf2 signaling in the basal expression, as well as the induction of antioxidants in pathological circumstances remains unclear.

Mitochondrial DNA copy number and mitochondrial gene expression are reduced in heart failure. Not surprisingly, concomitant downregulation of PGC-1α, Nrf2, and Tfam in the failing heart is observed. The mechanism by which pathophysiological cues downregulate PGC-1/NRF-1/Tfam expression have only begun to be resolved, but it is tempting to speculate that rescue of PGC-1/NRF-1/Tfam expression may have beneficial effects on cardiac function. Indeed, transgenic overexpression of Tfam in the heart ameliorates the decrease in mitochondrial DNA copy number and mitochondrial complex enzyme activities in the hearts and attenuates left ventricular remodeling and failure after myocardial infarction.

The novel concept that mitochondrial biogenesis seems to be triggered by mitochondrial ROS generation is intriguing. To move present knowledge toward more general applicability, the physiological and pathological relevance of mitochondrial ROS-mediated transcriptional and posttranscriptional activation of NRF-1 via AKT, in the setting of postneonatal normal growth, exercise-challenged, pressure-challenged, ischemic, and failing heart need to be clarified.

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None.

References


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Motoaki Sano and Keiichi Fukuda

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