On the Control of Metabolic Remodeling in Mitochondria of the Failing Heart

Joanne S. Ingwall, PhD

The metabolic phenotype of the failing heart may be defined as follows. Metabolism remolds in the failing heart, leading to a loss in energy reserve and the inability to increase ATP supply. Ultimately, this metabolic rigidity leads to a fall in ATP. The likely time line is decreased energy reserve via the phosphotransferase reactions (creatine kinase [CK] and adenylate kinase) leading to increases in ADP and AMP, triggering an increase in glycolysis. Although the contribution of glycolysis to overall ATP synthesis increases at least in the hypertrophied heart, glycolytic reserve is limited. Importantly, as heart failure evolves, ATP synthesis from oxidation of both endogenous and exogenous fatty acids by mitochondria, the major source of ATP in the heart, falls.

Remodeling of the failing myocardium is controlled by energy sensors such as AMP that lead to changes in phosphorylation state (as well as other chemical modifications) of many proteins for short-term preservation of ATP and by activation of transcription factors that coordinately control long-term remodeling of entire ATP synthesis and utilizing pathways.

Given that the requirement for ATP for all metabolic processes and for cell viability is absolute, a renewed interest in metabolism has led to identification of the molecular links between physiological and metabolic stimuli and the regulation of gene expression in the heart. We not only have identified the metabolic targets of specific nuclear receptors and DNA-binding transcriptional activators but also are beginning to learn how their signals are amplified and sustained to remodel metabolism.

Transcription is activated when transcriptional activators, including peroxisome proliferator-activated receptors, estrogen receptors, retinoid receptors, nuclear respiratory factors, and myocyte-enhancing factor-2 (MEF-2) form protein-protein complexes with the peroxisome proliferator-activated receptor-γ coactivators, namely PGC-1α and β, tethering PGC-1s to DNA (Figure). When complexed with the transcription activators, PGC-1s activate genes encoding proteins comprising entire metabolic pathways that control ATP synthesis in mitochondria (fatty acid uptake, β-oxidation, oxidative phosphorylation, the Krebs cycle, and electron transport chain), phosphoryl transfer (sarcomeric mitochondrial CK and adenine nucleotide transporter), glucose uptake and utilization, and ATP-utilizing proteins (Figure).

PGC-1α is itself regulated. For example, the cyclin-dependent kinases Cdk9 and Cdk7 target PGC-1α, thereby conferring additional specificity for the transcriptional control of ATP synthesizing and utilizing reactions. Other known regulators of PGC-1α in striated muscle include p38 mitogen-activated protein kinase, calcineurin A/calmodulin-dependent protein kinase II (CaMKII), possibly AMP-activated protein kinase (AMPK), and humoral factors. Evidence suggests that PGC-1α may be regulated differently in different tissues. Given its important role in regulating metabolism, knowing how the level of PGC-1α changes in the failing heart and how it is regulated are crucial for our understanding of metabolic control at a basic level and also how to develop new metabolic-based therapies for the failing heart. The article entitled “Control by Circulating Factors of Mitochondrial Function and Transcription Cascade in Heart Failure: A Role for Endothelin-1 and Angiotensin-II” by Garnier et al in this issue makes substantial contributions to our understanding of the control of mitochondrial function in the failing heart, a major step in this process.

The overall hypotheses tested in this article are that angiotensin-converting enzyme inhibition (ACEI) protects against reduced oxidative capacity in the failing myocardium and that this may be mediated by circulating hormones. The rationale is based on 2 observations: circulating hormones such as endothelin-1 (ET-1) are hyperactivated in heart failure patients and, as shown in previous work by this group, ACEi treatment was found to correct mitochondrial defects in skeletal muscle of heart failure patients. The specific hypotheses tested were (1) myocardial mitochondrial oxidative capacity is lower in ACEI-treated heart failure patients, (2) ACEi therapy protects myocardial mitochondrial function by activating PGC-1α expression, and (3) hormonal signals induce the PGC-1α transcription cascade. Three sets of experiments were performed.

Human Myocardium

Biopsy specimens from myocardium from 20 patients with end-stage heart failure (caused either by coronary artery disease or by nonischemic cardiomyopathy) who underwent...
transplantation, from nonfailing myocardium obtained from brain-dead accident victims, and from open-heart surgery patients (total n = 17) were analyzed for PGC-1α content, mitochondrial oxidative capacity, and activities of key mitochondrial enzymes, namely citrate synthase (CS) in the Krebs cycle and cyclooxygenase IV in the respiratory chain as well as CK isozymes located both in the cytosol and the mitochondria. All patients were on ACEi therapy; a subset was also treated with β-blockers.

PGC-1α protein content was ≈34% lower in myocardium from patients with end-stage heart failure than in nonfailing myocardium. Measuring amounts of this nonabundant protein has proven to be challenging; previous measurements have been made for experimental heart failure models (including by this group of investigators7). Given the many examples of lack of concordance between changes in mRNA levels and changes in protein amounts, these measurements for PGC-1α protein amounts in normal and failing human myocardium are welcome. Is a decrease of ≈34% sufficient to account for the changes in metabolic reserve in the failing myocardium? It is difficult to extrapolate from the phenotype defined for PGC-1α knockout mouse hearts showing the requirement of PGC-1α for normal mitochondrial function,8,9 but it seems highly likely that a chronic decrease in this master regulator of gene transcription contributes to the molecular remodeling that occurs in the failing myocardium.

Using skinned fibers, Garnier et al13 also report that maximum mitochondrial oxidative capacity in failing myocardium was ≈25% lower than for nonfailing hearts. Again, this measurement has been difficult to make, even in experimental animal models. Gong et al10 made this measurement in intact hearts in a failing swine model, concluding that oxidative capacity to supply ATP needed for an acute increase in work had reached maximal levels in failing hearts (ie, had no further energy reserve) but not in hypertrophied or normal hearts. It is possible that the decrease in mitochondrial oxidative capacity falls only at end-stage failure.

CS, cyclooxygenase IV, and CK isozyme activities, expressed as activity normalized to total protein, are all 40% to 50% lower, in good agreement with previous results (for example, see Ref. 11). All too few studies report enzyme activity results, even though this is the property we need to know to determine whether protein function is abnormal. A study by Scheubel et al12 in which mitochondrial enzyme activities were found to be unchanged in human failing hearts, normalized activities to CS activity. Importantly, the data presented by Garnier et al13 show that CS, a good marker of mitochondrial mass, also decreased. Normalizing cyclooxygenase and CK activities to CS activity in the Garnier et al study would show the same apparently misleading result. The observation that the enzyme activities all decrease to a similar extent suggests that the mitochondria that are present have near-normal composition. It is important to emphasize that these changes were found in myocardium from patients on ACEi therapy. These results suggest that ACEi therapy as currently used is not sufficient to protect the already failing myocardium fully from mitochondrial dysfunction, although it is possible that the dysfunction may have been worse without ACEi. Because a subset of patients treated with β-blockers showed no differences from ACEi alone, the change in mitochondrial dysfunction was independent of β-blockade.

Rat Model of Failure
The authors then made comparable measurements in a rat heart model of failure caused by myocardial infarction with and without ACEi. ACEi therapy did not fully protect the hearts from a fall in PGC-1α, decreased mitochondrial oxidative capacity, or enzyme activity changes, recapitulating the human heart failure phenotype. The trends, however, are close to full protection for the enzyme activities measured. Because perindopril was supplied early after ligation, whether ACEi therapy reverses or prevents defects in mitochondrial oxidative capacity remains to be fully tested.

Rat Ventricular Myocytes
The next step taken was to define the effects of humoral factors known to be involved in heart failure on transcriptional control of mitochondrial protein expression and the PGC-1α transcription cascade in isolated adult rat ventricular cells. ET-1, angiotensin II, phenyephrine, aldosterone, and isoproterenol were tested. Exposing cells to ET-1 recapitulated the heart failure phenotype with regard to lower cyclooxygenase IV activity and lower expression of the transcriptional regulators PGC-1α, nuclear respiratory factor-2α, and mito-
Mitochondrial Dysfunction in Failing Heart

Ingwall

Disclosures

None.

References


Key Words: heart failure remodeling
On the Control of Metabolic Remodeling in Mitochondria of the Failing Heart
Joanne S. Ingwall

Circ Heart Fail. 2009;2:275-277
doi: 10.1161/CIRCHEARTFAILURE.109.885301
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/2/4/275

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org/subscriptions/