Energy at heart: matching demand with production

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This editorial refers to ‘Mitochondrial transcription factors TFAM and TFB2M regulate Serca2 gene transcription’ by A. Watanabe et al., pp. 57–67, this issue.

How are energy-consuming processes matched with energy supply in constantly working heart muscle cells? A new piece in the puzzle of myocardial gene regulation indicates that two main inducers of energy production also increase the abundance of a major consumer. Watanabe et al.¹ convincingly demonstrate that mitochondrial transcription factors A (TFAM) and B2 (TFB2M) not only stimulate mitochondrial biogenesis, but also induce transcription of the Serca2 gene, which encodes the sarco-endoplasmic reticulum calcium ATPase type 2a (SERCA2a). Their findings are potentially important, since energy depletion is a major problem in the failing heart² and maintaining SERCA2a activity is vital for contractile function.³

Several lines of evidence from neonatal rat cardiomyocyte cultures and a rat experimental myocardial infarction model led to the conclusion that transcription of the Serca2 gene is regulated by TFAM and TFB2M,¹ which were previously thought to be specific for mitochondrial gene regulation. First, both transcription factors localize to the nucleus and not only to mitochondria, even though none of them has classical nuclear localization signals. There they bind to the 5′ regulatory region of the Serca2 gene, at the −122 to −114 and the −122 to −117 nt positions, respectively, and have no mutual additive or synergistic effect. Although binding is close to the regulatory site of SP1, another stimulator of Serca2 transcription, the factors seem to act independently. Overexpression of TFAM and TFB2M by transfection increases transcriptional activity about two-fold, and ablation by siRNA reduces activity to less than half. Accumulation and reduction of the factors occur in the nucleus and mitochondria, with no preferential change in either location,¹ and co-ordinately change the levels of specific mitochondrial proteins and ATP in cardiac myocytes.

How well do the results from cell culture translate to relevant in vivo experiments? As expected, the level of Serca2a mRNA is ~50% lower in rats with heart failure 5 months after myocardial infarction compared with sham-operated controls,¹ faithfully mimicking findings in heart failure patients.⁵ Cardiac content correlates significantly with mRNA levels of TFAM and TFB2M and with selected mitochondrial mRNA. These co-ordinate changes in Serca2 and mitochondrial gene products correlated significantly with physiological measures of in vivo systolic and diastolic cardiac function (Emax and τ, respectively), indicating that the extent of reduced transcription depends on the severity of cardiac dysfunction. Further cardiac myocyte culture experiments showed that mimicking the milieu interne of heart failure, either by adrenergic stimulation (norepinephrine) or by reactive oxygen species (hydrogen peroxide), significantly reduces Serca2 gene transcription. Overexpression of TFAM and TFB2M partially prevents the reduction of Serca2 and mitochondrial genes, pointing to the transcriptional regulators as potential targets for drug therapy.

Is there any other evidence that co-ordinately increasing SERCA2a function and mitochondrial biogenesis might work as a therapy for heart failure? Many successful interventions have been performed to selectively increase SERCA2a function in failing hearts, either by adenovirus-mediated gene transfer of or by interfering with its regulator phospholamban.⁴ In rat models, SERCA2a gene transfer improves systolic and diastolic cardiac function and abrogates ventricular arrhythmias induced by ischaemia and reperfusion. In human ventricular cardiomyocytes, overexpression increases calcium transport and enhances contraction and relaxation velocity. A platform for potential clinical translation has been laid by dose-dependent improvement of cardiac function in sheep with pacing-induced heart failure.⁴ Increasing SERCA2a activity by suppressing the inhibitory effect of phospholamban restores cardiac function in several small animal models. However, dilated cardiomyopathy at a young age in humans with mutations suggests that chronic phospholamban ablation may not be beneficial.³

Since metabolic impairment in heart failure is closely related to transcriptional control of mitochondrial biogenesis,⁵ targeting the transcription factors involved may provide a novel therapeutic strategy. Reduced cardiac remodelling and dysfunction after myocardial infarction in transgenic mice overexpressing TFAM gave a first proof-of-principle.⁶ Further evidence of its central role was provided by pathological hypertrophy and increased mortality in mice with cardiac-specific TFAM knockout and rescue of the phenotype after crossing with mice harbouring a human TFAM transgene.⁷ Initially, the beneficial effects of TFAM were attributed to ameliorating the pathological processes associated with oxidative stress.⁸ Although

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this may certainly be the case, the observation that mitochondrial transcription factors TFAM and TFB2M co-ordinately regulate Serca2 transcription suggests that increased SERCA2a function may be an additional mechanism to improve cardiac function.\(^1\)

Interestingly, gene transfer may not be the only way to increase mitochondrial biogenesis and SERCA2a function. A recent study demonstrated that exercise training attenuates the decrease in TFAM and re-establishes respiration and other mitochondrial functions in rats with long-term severe hyperglycaemia.\(^9\) In rats with heart failure, high-intensity interval training also reverses the reduction in SERCA2a; restores cardiomyocyte contractility, relaxation, and calcium handling; and diminishes pathologic hypertrophy and natriuretic peptide expression.\(^10\) These changes were associated with a substantial increase in work performance and peak oxygen uptake during treadmill exercise. A small, randomized clinical trial suggests that exercise may yield similar results in heart failure patients. A 12-week programme of interval training substantially increased work capacity and oxygen uptake and reduced left ventricular remodelling and circulating natriuretic peptide, and the magnitude of change exceeded those obtained by any cell or gene therapy so far.\(^11\) For obvious reasons, further studies are needed to clarify whether reverse remodelling in response to exercise training is associated with regulation of mitochondrial transcription factors and improved SERCA2a function.

In summary, the observation that mitochondrial transcription factors TFAM and TFB2M co-ordinately induce mitochondrial biogenesis and Serca2 expression\(^1\) not only proposes a mechanism by which energy production and consumption may be matched. It also suggests an additional explanation for beneficial effects in heart failure—by contributing to better myocardial calcium handling and contractility. Although the results point to potential therapeutic targets and may shed light on the effects of exercise, more pieces are needed to complete the fascinating puzzle of myocardial metabolism in heart failure.

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**References**