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EDITORIAL COMMENT

# Mitochondrial Calcium Flux—Friend or Foe in Chronic Heart Failure?*

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In energetically demanding tissues such as the heart, cellular function is fueled almost exclusively through the generation of mitochondrial adenosine triphosphate (ATP). Cardiomyocytes have variable energetic needs that can shift rapidly during physiological transitions such as sudden physical exertion, requiring ATP production to be fine-tuned to match cardiac demands. As such, cardiomyocytes must employ mechanisms that enable rapid increases in mitochondrial function to coordinate cellular energetic production with cardiac workload. One such mechanism involves the modulation of mitochondrial calcium signaling. Calcium is particularly well-suited to regulate cardiac mitochondrial function, as it activates muscle cell contraction and thus is intimately tied to cardiac workload. It has long been known that entry of calcium into the mitochondrial matrix up-regulates metabolic flux (and, by extension, increases ATP production), and does so through the stimulation of multiple dehydrogenases within the tricarboxylic acid cycle.[1] Although mitochondria had been known to transport calcium since the early 1960s,[2] the genetic identity of the calcium transport system, termed the mitochondrial calcium uniporter (MCU) came to light almost 50 years after these initial observations.[3,4] Since the identification of the MCU, various groups have sought to identify the role of mitochondrial calcium transport across models of disease, including cardiovascular pathologies such as chronic heart failure.

Despite the central importance of calcium to cardiomyocyte function, the role of mitochondrial calcium uptake in cardiovascular pathology remains controversial. Studies examining genetic alterations of MCU in mouse models have shown paradoxical trends, with at least one study indicating that increasing MCU expression reverses heart failure,[5] with others suggesting that down-regulation of MCU protects against the development of cardiovascular disease.[6,7] In this issue of *JACC: Basic to Translational Science*, Alves-Figueiredo et al[8] address this controversy by demonstrating that decreased MCU function alleviates multiple hallmarks of cardiovascular pathology, including hypertrophy, remodeling, and inflammation.

Based on the observation that MCU expression increases in response to chronically increased workload after transaortic constriction surgery, Alves-Figueiredo et al[8] predicted that maladaptive responses to cardiac injury would lead to the increased energetic demand, up-regulation of the MCU, and subsequent mitochondrial calcium overload. Alves-Figueiredo et al thus hypothesized that elevated MCU expression, or increases in mitochondrial calcium, would drive pathological hypertrophy and promote the progression to heart failure. To test this hypothesis, they employed models of angiotensin II (ANGII)-induced dysfunction in H9C2 rat cardiac ventricular myocytes. Using RNA interference-based approaches, the investigators demonstrated that knockdown of MCU prevents ANGII-stimulated cardiomyocyte hypertrophy and blunts the up-regulation of select messenger RNA transcripts associated with cardiac remodeling. Further investigation showed that knockdown of MCU prevented calcium overload and opening of the mitochondrial permeability transition pore and suppressed the accumulation of mitochondrial reactive oxygen species in basal and ANGII-treatment conditions. To confirm their results, Alves-Figueiredo et al used the

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well-characterized compound Ru360 to inhibit MCU function, which led to a similar suppression of ANGII-mediated pathological phenotypes in H9C2 cells. To determine the role of mitochondrial calcium in these responses, the investigators targeted a second regulator of mitochondrial calcium levels, $Na^+/Ca^{2+}$ exchanger (NCLX). Because NCLX functions to exchange $Ca^{2+}$ for $Na^{2+}$, its loss would lead to the accumulation of calcium in the mitochondrial matrix. Alves-Figueiredo et al demonstrate that pharmacologic inhibition of NCLX increased the hypertrophic response to ANGII and mitochondrial reactive oxygen species levels while inducing transcriptional changes associated with pathologic remodeling, even in conditions with diminished MCU expression. Collectively, these data suggest that the accumulation of mitochondrial calcium promotes cardiac dysfunction.

Importantly, Alves-Figueiredo et al[8] translated these insights in vivo, where they found that MCU protein expression increased in mice chronically exposed to ANGII. Permeabilized cardiomyocytes from animals with ANGII-induced heart failure showed increased mitochondrial $Ca^{2+}$ levels, and lysates from this model revealed a significant correlation between MCU expression and heart weight. Finally, the investigators examined MCU expression via immunohistochemistry in tissues from patients with heart failure. Impressively, 96% of tissues from patients with heart failure showed elevated MCU transcript levels relative to nonfailing cardiac tissue, and MCU expression significantly correlated with severity of disease; MCU transcript level inversely correlated with ejection fraction but positively correlated with left ventricular dimensions and measures of hypertrophy. Finally, the investigators analyzed tissue samples from a small cohort of patients that underwent surgical implantation of a left ventricular assist device to reduce cardiac workload. Remarkably, left ventricular assist device implantation significantly diminished MCU transcript levels in patients relative to their preintervention state, suggesting that the human heart can dynamically coordinate MCU expression with cardiac demand.

Whereas this study strongly links elevated mitochondrial calcium levels to cardiac pathology, some questions remain, particularly given the contradictory findings of MCU expression and its influence on the progression of heart failure. It is worth noting that Alves-Figueiredo et al[8] rely heavily on modeling cardiac dysfunction through ANGII treatment, and it is possible that other pathological stimuli would differentially influence mitochondrial calcium function and heart failure progression. However, as noted by the investigators, the strong correlation between MCU transcript expression and cardiac pathology in a cohort of human patients with heart failure—each with their own unique disease onset and progression—argues against an ANGII-dependent mechanism and rather suggests that elevated mitochondrial calcium generally correlates with heart failure progression.

Finally, it is worth noting that the pharmacologic targeting of mitochondrial calcium may be challenging due to the need for precise modulation of calcium levels. Whereas Alves-Figueiredo et al[8] show that limiting calcium influx through RNA interference-mediated ablation of MCU thwarts ANGII-induced pathologies in cardiomyocytes, their knockdown efficiencies were incomplete and hovered around 50% of wild-type levels. This is notable, because full loss of MCU may also trigger cellular challenges, such as an inability to properly buffer $Ca^{2+}$. Importantly, rare cases of hypocalcemia have been documented and can also lead to heart failure,[9] underscoring the importance of properly calibrated $Ca^{2+}$ flux in normal cardiac function. Despite these potential difficulties, this study highlights the therapeutic possibilities of calibrating mitochondrial calcium influx to address chronic heart failure. Notably, one recent study identified U.S. Food and Drug Administration-approved drugs that modulate MCU activity in isolated myocytes.[10] Given the results of Alves-Figueiredo et al,[8] a subset of these compounds may have therapeutic value if repurposed for the treatment of chronic heart failure.

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