

Failed Power Plant Turns Into Mass Murder New Insight on Mitochondrial Cardiomyopathy

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Mitochondria are known as the powerhouse of the cell. For a high-energy-consuming organ, such as the heart, continuous ATP production via oxidative metabolism in the mitochondria is essential. Apart from ATP generation, mitochondria are also key to the regulation of cellular metabolism, calcium homeostasis, and reactive oxygen species (ROS) generation.¹ Mitochondrial dysfunction has been strongly implicated in a variety of cardiovascular diseases including ischemic heart disease and heart failure. Furthermore, a large portion of mitochondrial disease patients, a condition caused by mutation of genes for mitochondrial proteins, develop cardiomyopathy indicating a causal role of mitochondria in cardiac dysfunction. Given its significant role in the pathogenesis and the current lack of effective therapy for mitochondrial dysfunction, there is a clear need for discovery and innovation in mitochondrial medicine.^{2,3}

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It is well established that the fetal heart relies heavily on glycolysis for energy metabolism. A switch from glycolysis to oxidative metabolism in the early postnatal period is associated with explosive mitochondrial biogenesis.^{4,5} The switch is critical for the postnatal maturation of the heart. Loss of PGC-1 α/β (peroxisome proliferator-activated receptor gamma coactivator), the powerful transcriptional regulators of mitochondrial biogenesis, in perinatal and postnatal periods, results in lethal cardiomyopathy.^{6,7} The role of mitochondria in the embryonic cardiomyocytes is, however, less explored. Recent studies using pluripotent cell-derived cardiomyocytes have suggested intriguing functions of mitochondria beyond energy provision in the regulation of cardiomyocytes maturation.^{6,8-10} In this issue of *Circulation Research*, Zhang et al¹¹ described a novel mechanism by which mitochondrial defect inhibited cardiomyocyte proliferation during fetal and early postnatal periods (Figure). They further proposed that targeting such a mechanism could be therapeutic for cardiac dysfunction caused by mitochondrial defect.

The study by Zhang et al used mice and cardiomyocytes with inactivation of mitochondrial Tfam (transcription factor A) as a model system. Tfam is a nuclear genome-encoded

protein responsible for the transcription and replication of mitochondrial DNA. Tfam deficiency depletes proteins encoded by mitochondrial DNA leading to defective electron transport chain of the mitochondria. The authors found that cardiac-specific Tfam deficiency led to embryonic lethality at day E16 associated with myocardial hypoplasia. Elegant genetic manipulation and fate-mapping techniques demonstrated that the myocardial hypoplasia was caused by impaired proliferation and increased apoptosis of cardiomyocytes. Interestingly, the authors did not find evidence of energy deficiency in the fetal cardiomyocytes with Tfam deletion. Instead, their transcriptome analysis identified the activation of DNA damage response (DDR) pathway as the culprit. They went on to demonstrate that elevated mitochondrial ROS production in Tfam-deficient cardiomyocytes triggered DDR, which in turn suppressed cardiomyocyte proliferation (Figure).

The observations by Zhang et al reveal a novel mechanism through which mitochondrial function regulates cardiomyocytes proliferation during development. Defective oxidative phosphorylation, even though did not affect energy supply in embryonic cardiomyocytes, led to excessive ROS generation and inhibition of cell cycle activity. The authors, therefore, suggested that inhibition of cardiomyocytes proliferation could be a potential mechanism for cardiac dysfunction in mitochondrial disease patients. To test the therapeutic implication, mito-TEMPO and WEE1 kinase inhibitor were used to suppress ROS and DDR, respectively, in Tfam-deficient hearts. In mice with Tfam ablation induced at birth, treatment with either compound in the first week of postnatal period could rescue the myocardial hypoplasia phenotype and improved cardiac function. Notably, targeting the same pathway in the second week after birth had little beneficial effects. These results are significant because they demonstrate the causality of ROS and DDR in the loss of cardiomyocytes proliferation associated with Tfam deficiency. In addition, the study shows that the therapeutic window of mito-TEMPO and WEE1 kinase inhibitor coincides with the neonatal period during which cardiomyocytes retain cell cycle activity. The observation further supports the notion that cardiac dysfunction in Tfam-deficient hearts is attributable, at least partially, to the inhibition of cardiomyocytes proliferation in neonatal hearts.

It has been reported that the loss of regenerative capacity in mammalian heart coincides with cell cycle arrest induced by ROS and DDR at postnatal day 7.¹²⁻¹⁴ It is, thus, likely that the switch to oxidative metabolism after birth in normal heart induces mitochondrial ROS production and DNA damage response, which leads to cardiomyocyte cell cycle arrest. In those studies, the regulation of cell cycle exit by ROS is further supported by the evidence that postnatal hypoxemia

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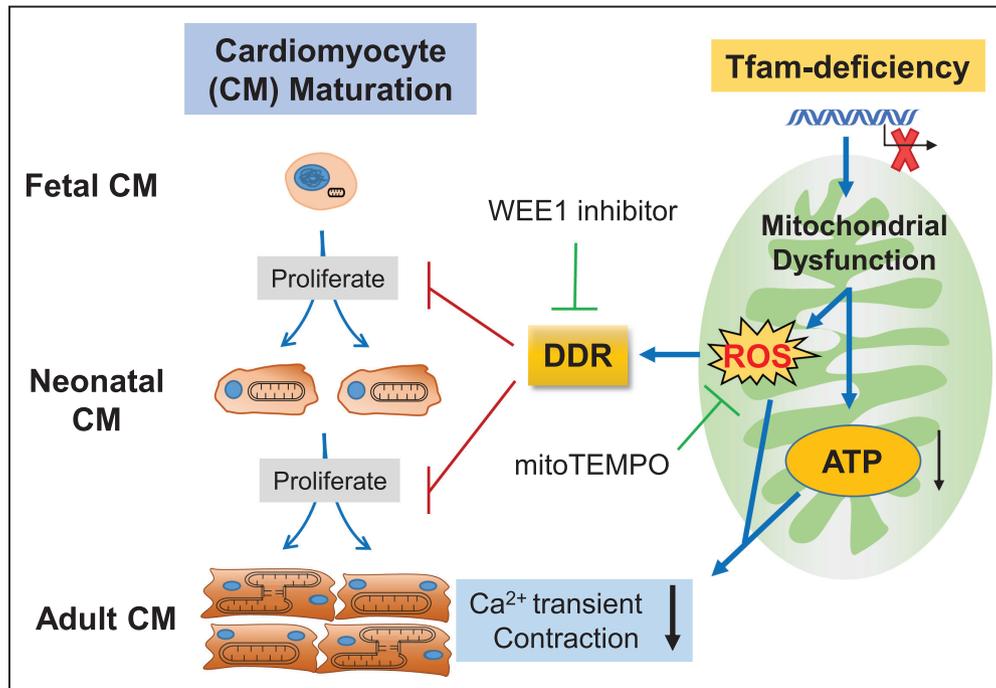


Figure. Mechanisms linking mitochondrial dysfunction and cardiomyocyte proliferation during development. Cardiac development involves proliferation of cardiomyocytes (CM) from fetal stage throughout the early postnatal period. The maturation of CM involves increases in cell size, development of sarcomere structure and contractile apparatus, and maturation of mitochondria. Zhang et al have identified that inactivation of Tfam (transcription factor A), a nuclear-encoded protein that controls mitochondrial DNA transcription and replication, causes mitochondrial dysfunction and embryonic lethality associated with myocardial hypoplasia. Mitochondrial dysfunction triggers excessive reactive oxygen species (ROS) production and consequently activation of the DNA damage response (DDR) pathway, which inhibits CM proliferation during prenatal and early postnatal periods. ROS scavenging or DDR inhibition by mito-TEMPO and WEE1 inhibitor, respectively, rescue the proliferation arrest. Increased ROS and reduced ATP level, caused by impaired mitochondrial function, lead to diminished contractility of mature CMs.

inhibits DNA damage and prolongs the postnatal window of cardiomyocytes proliferation, whereas postnatal hyperoxemia potentiates DNA damage and early cell cycle arrest.¹² Taken together, activation of DDR seems to be a shared mechanism by which mitochondrial function regulates cell cycle activity.

Another interesting observation made in the study was that deletion of Tfam in neonatal heart did not affect cell size, T-tubule structure, or sarcomere morphology of cardiomyocytes. These findings suggest that mitochondria are dispensable for the maturation of contractile apparatus in the postnatal cardiomyocyte. It is, however, not clear whether mitochondrial function is required for the formation of sarcomeres during embryonic development. Despite the apparent normal contractile machineries, Tfam-deficient cardiomyocytes showed impaired contractility and reduced calcium transient, suggesting that mitochondrial function is crucial for the function of mature cardiomyocytes.

The finding by Zhang et al also provides a conceptual basis for novel therapy of mitochondrial cardiomyopathy. However, several limitations of the model must be taken into account when considering the translational potential of these findings. Tfam deletion is embryonic lethal. Mutations of similar severity are unlikely seen in live birth. The authors tested their hypothesis by deleting Tfam at postnatal day 0, which would not occur in patients. Nevertheless, it is possible that other mutations of ETC (electron transport chain) proteins could spare cardiomyocytes proliferation during fetal development but generate ROS and trigger DDR at neonatal stage. These patients would

benefit from the therapy immediately after birth. Antioxidant therapy in mitochondrial disease has limited success to date. The present study suggests that the timing of the therapy can be critical in cardiomyopathy. Therefore, it is important to identify the target patient population that may benefit from the treatment during early neonatal period. Furthermore, because chronic hypoxia suppress mitochondrial ROS and DDR,¹⁵ it will be interesting to test whether combining hypoxia treatment with inhibitions of ROS or DDR pathway will have additional benefits for mitochondrial cardiomyopathy.

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Disclosures

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