Is the Therapeutic Window for Mitochondrial ROS Half-Open or Half-Closed?
Mixing Mitophagic Metaphors

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The adult hearts rely on oxidative phosphorylation within the mitochondria as the primary source of energy production. A potential deleterious byproduct of oxidative phosphorylation is the generation of reactive oxygen species (ROS), and thus cardiac mitochondria are currently appreciated as the major source of ROS within the heart. Subsequently, elevations in mitochondrial ROS production have been identified as a key mediator of many of the pathological changes that occur in the failing heart. Yet, therapeutic strategies to reduce ROS have failed to yield outcomes that might have been expected based on the supporting data, and it is important that we continue to expand our understanding of ROS signaling in the heart in order that we might improve treatment outcomes. Recent work by Song et al now demonstrates that although attenuating ROS production to normal levels via expression of mitochondrial targeted catalase (mCAT) in a model of mitofusin (Mfn)-deficient cardiomyopathy promotes mitochondrial fitness, the super suppression of ROS with high mCAT fails to improve mitochondrial quality. High mCAT levels in this Mfn deletion model were instead related to impairment of secondary autophagic pathways associated with mitochondrial quality control. The implication of this finding is that the contribution of local mitochondrial ROS to mitochondrial degradation is an important component of mitophagy-dependent quality control. Song et al extend their findings to suggest a therapeutic window of ROS suppression.

ROS production increases in damaged mitochondria, and therefore, it is important that quality control mechanisms are in place to cull damaged mitochondria. Mitophagy is a specialized form of autophagy that maintains mitochondrial quality control in the heart. A principal component of mitochondrial culling through mitophagy is Mfn2. Mfn2, along with Mfn1, are outer mitochondrial membrane fusion proteins that serve multiple functions. Mfn1 and 2 tether mitochondria to the sarcoplasmic reticulum, facilitating close communication between the sarcoplasmic reticulum and the mitochondria; permit outer mitochondrial remodeling during mitochondrial fusion; and facilitate mitophagy. Phosphorylation of Mfn2 by the PTEN (phosphatase and tensin homolog)-inducible kinase 1 leads to parkin recruitment to damaged mitochondria and initiates mitophagic removal. Loss of Mfn2 expression in the heart leads to the accumulation of abnormal mitochondria and a delayed cardiomyopathy. In this issue of Circulation Research, Song et al have addressed the contribution of ROS to the delayed cardiomyopathy in the Mfn2 null mouse. ROS levels are elevated in the Mfn2 null mouse heart because of the reduced clearance of damaged mitochondria. To investigate the impact of mitochondrial ROS, Mfn2 null mice were crossed with mice expressing the mCAT. The protocol generated 2 different Mfn2 null/CAT models: 1 model expressing low levels of mCAT (Mfn2/lowCAT) and another model expressing mCAT at high levels (Mfn2/hiCAT). As expected, Mfn2 null mice developed a delayed cardiomyopathy and displayed reduced mitochondrial quality control.

In agreement with what might be expected from the classical free radical theory, the Mfn2/lowCAT hearts showed an improvement in cardiac function, reduced hypertrophy, and normalization of ROS production compared with Mfn2 null mice. Remarkably, however, the Mfn2/hiCAT mice displayed worsening cardiac function and a further increase in hypertrophy compared with Mfn2 null mice, despite ROS being reduced below levels measured in wild-type hearts. The differences in cardiac function could be partially explained by differences in mitochondria quality control.

Mitochondria quality control was improved in the Mfn2/lowCAT hearts, whereas it deteriorated further in the Mfn2/hiCAT hearts relative to the Mfn2 null mouse. This apparent inverse dose-response led the authors to propose the existence of a compensatory therapeutic window, illustrated in the Figure. Low levels of mitochondrial ROS were required to initiate compensatory autophagy to counteract the interrupted mitophagic signaling and loss of parkin recruitment to the mitochondria. Both the compensatory autophagy and the primary mitophagy were lost when mCAT was expressed at high levels in the Mfn2/hiCAT mouse, exacerbating the defect in mitochondria quality control that already exists in the Mfn2 null mouse.

Although the study by Song et al presents convincing evidence for a therapeutic window for compensatory ROS-dependent autophagy, the mechanism whereby high levels of ROS induce cardiomyopathy in the Mfn2 null mouse remains to be determined.

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

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Elevated Cyclophilin D regulates the opening of the mitochondrial permeability transition pore. One possibility is that elevated Cyclophilin D regulates the opening of the mitochondrial permeability transition pore. In the absence of Mfn2, damaged mitochondria accumulate, and there is increased reactive oxygen species (ROS) production. Although much of the ROS produced is detrimental to the cardiomyocyte and impairs cardiac function, low levels of ROS production are required to initiate compensatory autophagy. The goal of treatment in this model of interrupted mitophagy is to reduce the bulk of ROS production by the mitochondria (therapeutic target) while maintaining some ROS release to initiate compensatory recruitment of phagophores to the damaged mitochondria.

Figure. Mitochondria quality control under normal conditions and in the absence of mitofusin (Mfn) 2. Mitochondrial depolarization results in phosphorylation of Mfn2 and recruitment of Parkin to the damaged mitochondria. Parkin recruitment initiates mitophagy of the damaged mitochondria. In the absence of Mfn2, damaged mitochondria accumulate, and there is increased reactive oxygen species (ROS) production. Although much of the ROS produced is detrimental to the cardiomyocyte and impairs cardiac function, low levels of ROS production are required to initiate compensatory autophagy. The target of treatment in this model of interrupted mitophagy is to reduce the bulk of ROS production by the mitochondria (therapeutic target) while maintaining some ROS release to initiate compensatory recruitment of phagophores to the damaged mitochondria.

The corrective effect of low mCAT, but not high mCAT, expression suggests that despite the benefits of low level ROS in the Mfn2 null mouse, some ROS reduction is required to rescue the Mfn2 phenotype. No evidence was found for oxidative protein damage in the Mfn2 null mouse nor did knockout of cyclophilin D rescue the Mfn2 null mouse. Cyclophilin D regulates the opening of the mitochondrial permeability transition pore. One possibility is that elevated ROS production in the Mfn2 null mouse heart accelerates mitochondrial decay beyond the capacity for the compensatory autophagy or that high ROS production interferes with the compensatory autophagy (ie, ROS outcompeting ROS). In support of this later point, Song et al found that components of the autophagic pathway, autophagosome-associated p62/sequestome and processing of microtubule-associated protein light chain, were upregulated after the normalization of ROS levels in the Mfn2/lowCAT mouse heart, whereas the Mfn2/highCAT mouse heart showed no improvement. A little ROS production activates compensatory autophagy, but a lot of ROS production produces a more modest return. In addition to suggesting the presence of a therapeutic window for ROS suppression, Song et al have also potentially identified new avenues of investigation for identifying novel targets, whereby ROS is able to affect cellular signaling pathways and induce cardiac dysfunction.

There is an emerging body of work that supports the concept that low levels of ROS production from the mitochondria are important in maintaining cellular homeostasis, as well as the induction of protective signaling cascades in responses to stress. In the work of Song et al presented in this issue, the ROS-dependent induction of autophagy was a compensatory response to the dysregulation of normal mitophagic clearance. The data does not suggest a role for mitochondrial ROS in mitophagy or autophagy in the absence of stress. Expression of mCAT alone had no effect on cardiac function at either low or high levels, and both low and high levels of mCAT expression have successfully improved other models of heart failure. Overall, it would seem that in the absence of a defect in parkin-mediated mitophagy, there is not an additional compensatory role played by ROS. It will be interesting to see whether ROS generation can influence mitochondria quality control in other models of interrupted mitophagy.

Therefore, the notion offered by the findings of Song et al is a range of ROS activity that influences mitophagic regulation of mitochondrial quality in the diseased state, with a window of ROS activity that provides advantageous induction of mitophagy rather than promoting a vicious cycle of ROS production and mitochondrial dysfunction from which there is no return. The possibility of a controllable and beneficial level of ROS production in the face of impaired mitophagy, as shown in the Mfn2–deficient heart, is similar to the old metaphor of whether the glass is half-full or half-empty. Whether or not pathogenic stressors invoke mechanisms that respond to fine-tuning of mitochondrial ROS remains to be seen. The perspective on a beneficial window of mitochondrial ROS on mitochondrial quality control in remediating cardiomyopathies may well depend on the extent of an autophagic defect in the pathogenesis of the disease. Nevertheless, the concept demonstrated in rescuing hearts lacking Mfn2 with mid-range expression of mCAT provides valuable insights into the reciprocal and potentially self-regulating processes of mitochondrial dysfunction and quality control.

Disclosures

None.

References


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