Although research has identified extensive selenium-dependent functions in the human body, the role of selenium supplementation in cardiovascular disease remains uncertain. Our findings call for studies exploring possible favorable effects of selenium supplementation in the treatment of HF.

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Mitochondrial Unfolded Protein Response (UPR^{mt}) Activation in Cardiac Diseases

Opportunities and Challenges

As reported by Smyrnias et al. (1), pre-induction of mitochondrial unfolded protein response (UPR^{mt}) using nicotinamide riboside is sufficient to prevent cardiac dysfunction induced by chronic hemodynamic overload in rodents. These findings open up a new avenue for strategies targeting mitochondrial dysfunction to treat cardiovascular diseases (2) and raise important questions that should be addressed to pursue the UPR^{mt} activation as a feasible therapy.

First, the magnitude of UPR^{mt} activation observed by Smyrnias et al. (1) varies between a 0.3- and 10-fold increase among conditions (cell culture, mouse, and human data) in which UPR^{mt} activation seems to have no clear association with a phenotype (beneficial or detrimental). For example, chronic hemodynamic overload increases cardiac levels of UPR^{mt} markers ~50% (VS. a 30% increase in healthy nicotinamide riboside-treated animals) compared with control subjects. However, pre-induction of UPR^{mt} using nicotinamide riboside has a remarkable positive effect on mitochondrial and cardiac function upon hemodynamic stress. Considering the key role of nicotinamide adenine dinucleotide in cardiac physiology (3), the UPR^{mt}-dependent effect of nicotinamide riboside must still be determined.

Second, drugs used to treat cardiac diseases work mainly thorough inhibition of neurohumoral hyperactivation (i.e., angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, AT_1 antagonists), thereby minimizing the cardiac stress. Here, there is an intriguing and somewhat counter-intuitive situation in which both disease (or conditions mimicking the disease in culture) and treatment (measured according to messenger ribonucleic acid levels) improve the UPR^{mt} signal. Consequently, it becomes critical to dissect the extension and overlap of cardiac UPR^{mt} activation upon different interventions, thus contributing to a better understanding of its compensatory, deleterious, or neutral (associative) effects. This approach will be helpful to screen and develop drugs targeting cardiac UPR^{mt}. Other questions related to the effectiveness and toxicity of pharmacological cardiac UPR^{mt} activation (including transient vs. sustained activation or prevention vs. therapy), as well as its dependence on

mitochondrial dysfunction, also need to be addressed to define the best clinical need for such intervention. Finally, there will be a translational challenge finding molecules capable of boosting UPR^{mt} in failing human hearts, in which the UPR^{mt} is already hyperactivated.

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REPLY: Mitochondrial Unfolded Protein Response (UPR^{mt}) Activation in Cardiac Diseases

Opportunities and Challenges

We thank Dr. Bozi and colleagues for their interest in our work on the mitochondrial unfolded protein response (UPR^{mt}) in the murine and human heart (1). Our study showed that diverse stresses (e.g., neurohumoral agonists, hemodynamic overload) induce the UPR^{mt}, whereas its enhancement with small-molecule agents is protective against mitochondrial and contractile dysfunction in a model of hemodynamic overload. We also found a negative correlation between expression levels of UPR^{mt} genes in myocardial tissue and biomarkers of cardiomyocyte death and cardiac stress in patients with aortic stenosis, consistent with the notion that the UPR^{mt} may be protective in such patients.

Although Dr. Bozi and colleagues comment on the varied increase in UPR^{mt} markers, this outcome is not surprising because diverse disease stresses may have different impacts on mitochondrial protein folding. Our study was not designed to establish a dose-response relationship; what is more noteworthy is that activation of the UPR^{mt} was typically transient. This finding is common in conditions in which homeostatic stress responses are triggered but fail to sufficiently mitigate the stress. The finding that boosting the UPR^{mt} was beneficial is therefore entirely consistent with the transient nature of the endogenous UPR^{mt} response.

Inducing an increase in the extent of UPR^{mt} with nicotinamide riboside (NR), a nicotinamide adenine dinucleotide precursor, has been previously reported by several groups (2). NR may have multiple effects because of the importance of nicotinamide adenine dinucleotide in metabolism but at least part of its effect in cardiomyocytes involved the UPR^{mt} because its actions were dependent on Atf5, which has been identified as a major regulator of the mammalian UPR^{mt} (3). Although our findings are promising, we would caution against too simple a jump to discussion of potential therapeutic indications. More human studies are required to establish at what point during disease evolution is the optimal time for initiation of UPR^{mt}-boosting therapy. Cardiomyocyte and mitochondrial status may be heterogeneous in chronically stressed hearts, and preventing death of even a small proportion of cardiomyocytes may be sufficient to mitigate the development of heart failure. The most important take-home messages from our study are that the UPR^{mt} is a significant positive modulator of mitochondrial function and can in principle be boosted with agents such as NR.

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