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Response to Letter Regarding Article, "Integrated Stress Response Couples Mitochondrial Protein Translation with Oxidative Stress Control"

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Keywords

10114; 10118; 10133; 10136

In Response:

We appreciate the insightful comments from Belmadani and Matrougui on our recent study of the integrated stress response (ISR) in ischemic heart disease.[1]

The authors raise an important point regarding how cells balance the acute PERK/ISR activation which improves survival and chronic PERK/ISR elevation which triggers cell death. We agree with the authors that chronic activation of the PERK axis of the ISR may induce apoptosis during cardiac ischemia/reperfusion (I/R). In our study, we found that PERK and its downstream pathway is mainly activated in the acute phase of reperfusion. This signaling disappears rapidly, especially in mouse hearts *in vivo*. We therefore focused on the acute action of the PERK axis of the ISR. We found that activation of PERK right before reperfusion or at the time of reperfusion protects the heart against I/R injury. The underlying mechanism may involve selective decreases of mitochondrial-derived reactive oxygen species. However, it remains to be determined how the transition from acute to chronic ISR occurs. A recent study may provide some insights.[2] Kaspar et al. found that CHOP, a downstream transcriptional factor of the ISR, plays a rheostat role that attenuates prolonged ISR and prevents unfavorable metabolic alterations under mitochondrial dysfunction. CHOP is required to adjust ATF4 levels and keep ATF4-regulated transcriptional program under check. Failure of the governance by CHOP triggers the transition from acute to chronic ISR. On the other hand, we recognize that CHOP deletion improves cardiac response under I/R, as shown by Miyazaki et al. using a whole-body CHOP deficiency mouse model.[3] Future work is needed to determine whether CHOP plays a role in the transition of the ISR under cardiac I/R and whether cell type specific expression of CHOP may exert different roles in this process.

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Disclosures

None.

The second comment is regarding the role of endothelial cells (ECs) in cardiac I/R. We strongly agree with the authors that the crosstalk between ECs and cardiomyocytes (CMs) is critical in regulating heart function. In the heart, ECs constitute the majority of non-CMs, which likely play an important role in cardiac I/R. Hedhli et al. found that ECs-derived neuregulin protects CMs from I/R injury.[4] On the other hand, a recent study showed that ischemic CMs enhance angiogenesis and improve cardiac function by secreting paracrine factors.[5] These findings collectively highlight a two-way traffic mode of regulation between CMs and ECs in the heart, which is essential in maintaining cardiac function under I/R. Since the ISR is activated by I/R in both cell types, it will be important to examine whether the ISR participates in the crosstalk and if so, what the underlying mechanisms are. Therefore, Belmadani and Matrougui provide two important comments on our study. Illustration of the transition from acute to chronic ISR and the interplay between CMs and ECs under I/R may provide valuable insights to our understanding of the pathogenesis of reperfusion injury and to the identification of therapeutic targets against ischemic heart disease.

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