Correspondence

Response to Letter Regarding Article, “Toll-like Receptor-Mediated Inflammatory Signaling Reprograms Cardiac Energy Metabolism by Repressing Peroxisome Proliferator-Activated Receptor γ Coactivator-1 Signaling”

We appreciate the comments of Drs Siracusano and Girasole regarding our article characterizing the role of toll-like receptor 4–mediated inflammatory signaling in modulating cardiac metabolism.1 In their commentary, the authors suggest that suppression of mitochondrial fuel flux during inflammatory stress may initially serve to prevent cardiac myocyte damage by mechanisms such as reducing the generation of reactive oxygen species. This conceptual model is consistent with the notion of “metabolic hibernation,” which may serve as a cardioprotective response in the context of sepsis.2 Indeed, such hypotheses fueled our study to explore the effects of sepsis on myocardial substrate metabolism. Our results indicate the existence of an inflammatory-metabolic cross-talk mechanism that links activation of the toll-like receptor 4/nuclear factor-κB pathway to suppression of the peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1) gene regulatory circuit. However, do the observed metabolic derangements contribute to the cardiac dysfunction caused by sepsis? As outlined in the insightful letter written by Drs Siracusano and Girasole, our results and findings by others1,3,4 in mice and humans with sepsis strongly suggest that inflammation leads to myocyte lipid accumulation through the combined effects of impaired fatty acid oxidation (FAO) and increased fatty acid delivery to the myocyte. Consistent with the intriguing possibility that myocyte “lipotoxicity” contributes to septic cardiac dysfunction, we demonstrated that overexpression of PGC-1β in cardiac myocytes reduces lipopolysaccharide-induced myocardial lipid accumulation and rescues the ventricular dysfunction. The observed connection between toll-like receptor 4 signaling and PGC-1 coactivators defines a nodal point for the convergence of key pathways involved in inflammatory signaling, mitochondrial function, and myocyte lipid homeostasis. Notably, we found that restoring PGC-1β expression in cardiac myocytes reversed the untoward effects of lipopolysaccharide without modulating the inflammatory response, indicating that these pathways can be uncoupled. This latter observation suggests that the PGC-1 gene regulatory circuit should be considered as a candidate target for the prevention or treatment of heart failure caused by inflammation, including septic cardiomyopathy.

Disclosures

Dr Kelly received consulting fees for his advisory board relationships with Eli Lilly and Company and Johnson & Johnson.

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References

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