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Mitochondrial Dysfunction During Sepsis: Still More Questions Than Answers

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Keywords

Mitochondria; sepsis; ATP; cytochrome; respiration

Despite decades of research, there are few effective treatments that can be offered to septic shock patients other than antibiotics and supportive care [1]. Uncertainties relating to the pathogenesis of sepsis, and more specifically the cause of multiorgan dysfunction syndrome (MODS), the putative cause of death during sepsis [2, 3], remains an obstacle to progress on this front. Although most investigators agree that overwhelming activation of the innate immune response is an essential prerequisite for organ damage, strategies designed to modulate inflammation during sepsis have been disappointing [3]. A growing body of evidence links cytopathic events, particularly mitochondrial, to the development of organ dysfunction [4, 5] and death [4, 6] during sepsis. The first steps towards understanding this phenomenon is to better characterize the mechanisms of mitochondrial dysfunction in tissues and cells that are essential for survival.

Owing to breaches in the normal immune barriers (e.g., central venous access) and impaired immune responses, referred to as “immune paralysis”, septic patients are at particularly high risk of developing a second and frequently lethal “hospital-acquired” infection [7]. The cause of immune paralysis remains unclear; however, significant alterations in peripheral blood mononuclear cell bioenergetics have been recently reported in the context of human sepsis. In a very interesting study by Belikova *et al* it was shown that plasma derived from septic patients was sufficient to induce dramatic changes in mitochondrial function, including suppression of ADP-dependent (State 3) respiration and uncoupling of respiration, resulting in significantly reduced ATP production in peripheral blood mononuclear cells (PBMCs) [8]. In a related study by Calvano *et al* a genome-wide gene expression analysis of PBMCs conducted in humans treated with low-dose endotoxin showed marked suppression of multiple genes relating to mitochondrial oxidative phosphorylation, suggesting that altered PBMC bioenergetics is explained, at least in part, by a fundamental “reprogramming” of the cells in response to bacterial antigens [9]. The Calvano study provides an alternative to the prevailing paradigm linking suppression of bioenergetic pathways to mitochondrial damage (e.g., oxidative stress) [10]. Indeed, it is likely that mitochondrial pathology during severe sepsis represents the combined effects of cytopathic and genetic mechanisms, culminating in compromised bioenergetic capacity and impaired cell function.

In this issue of *Critical Care Medicine*, Japiassu *et al* [11] provide novel insights into the pathogenesis of mitochondrial dysfunction in immune cells during severe sepsis. Intact

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PBMCs derived from patients within 48 hrs of ICU admission for severe sepsis were isolated and permeabilized for subsequent mitochondrial analyses and the results were compared to a non-infected post-operative ICU control group. Using succinate as the substrate for mitochondrial electron transport, they observed reduced State 3 respiration in septic shock patients. They did not detect significant “uncoupling” of respiration during sepsis, as reflected by their ability to inhibit oxygen consumption with the addition of oligomycin, a potent inhibitor of F1Fo ATP synthase essential for the formation of ATP at the expense of the electrochemical gradient. Altered State 3 respiration was apparently unrelated to impaired maximal electron transport, as this was equal in both cohorts in the presence of a respiratory uncoupling agent (FCCP), but was associated with a statistically significant 50% reduction in F1Fo ATP synthase activity, as reflected by the elegant oligomycin titration experiments. Finally, and in keeping with previous studies linking impaired mitochondrial function in muscle tissue to sepsis mortality, impaired mitochondrial respiration in PBMCs was associated with increased sepsis mortality. The authors reasonably conclude that altered mitochondrial respiration could contribute to so-called “immune paralysis” during sepsis [3].

A number of methodological factors could have influenced the results of this study, and could also explain why their results differ from previous reports. The selection of succinate as the electron donor bypasses complex I, a well-established target of functionally relevant post-translational modifications (e.g., nitration, nitrosylation) during sepsis [12]. Serendipitously, ignoring the effects of Complex I may have helped to unveil the novel role of F1Fo in this study. In this regard, reliance on oxygen consumption to determine F1Fo ATP synthase “content”, as shown in Figure 4 of the current study [11] is problematic in that ADP-dependent oxygen consumption does not account for the presence of damaged F1Fo molecules (e.g., extramitochondrial liberation of the F1 subunit of ATP synthase), such as occurs in the setting of acute endotoxemia [13]. Free F1 complex is potentially harmful in that it efficiently hydrolizes ATP and could thereby contribute to intracellular ATP depletion. Another variable to consider is the effects of circulating factors during sepsis which are shown to uncouple mitochondrial respiration in PBMCs [8] and platelets [14]. These direct effects of plasma emphasize the importance of the *in vivo* microenvironment as a determinant of cell function in the context of sepsis, and this variable is removed during the analysis of isolated cells or mitochondrial preparations. Finally, given the diverse disease mechanisms and phenotypes coexisting under the moniker of “critical illness”, the selection of any critically ill control group introduces some degree of bias. The authors’ selection of a cohort of uninfected post-operative patients is reasonable: however, the severity of illness score of the post-operative group was significantly lower than that of the septic shock group leaving the possibility that these findings are not specific to an infectious insult, but rather to the physiology of critically ill patients in general.

Despite these limitations, this study emphasizes the potential importance of the F1Fo ATP synthase complex during sepsis. This complex is interesting in that it can variably produce or consume ATP, depending on the conditions. The production of ATP is favored by the availability of substrate (ADP) and by a greater electrochemical gradient. On the other hand, the hydrolysis of ATP is regulated by mitochondrial ATPase inhibitor protein (IF1), which is shown to be depleted in animal models of sepsis [15]. Thus, the conditions of sepsis represent a “perfect storm” for impaired F1Fo ATP synthase-dependent ATP production, wherein F1Fo ATP synthase function is suppressed (current study [11], mitochondrial respiration is uncoupled thereby reducing the electrochemical gradient [8], and IF1 is depleted favoring ATP hydrolysis [15]. Given the strong association of altered PBMC F1Fo ATP synthase activity with clinically important outcomes (organ failures, mortality), and the relative accessibility of blood samples in the clinical setting (e.g., compared to muscle

biopsies [6]), PBMC F1Fo ATP synthase activity may prove to be a valuable prognostic tool in the setting of sepsis.

Despite steady progress towards defining the mechanisms of mitochondrial dysfunction during sepsis, a number of questions remain unanswered. Most importantly, is mitochondrial dysfunction the proximal cause of organ failure or is it merely a mechanism to avert further cell damage relating to excessive mitochondrial oxidant production [16], or to suppress potentially self-destructive immune responses? Given the vital roles played by mitochondria in the regulation of vital cell functions, including energy metabolism, apoptosis pathways, cell signaling and proliferation [17], it is very likely that mitochondria are mechanistically involved in both the failure and recovery of cells/organs in the context of sepsis.

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References

1. Barochia AV, Cui X, Vitberg D, et al. Bundled care for septic shock: an analysis of clinical trials. Crit Care Med. 2010; 38:668–678. [PubMed: 20029343]
2. Marshall JC. Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med. 2001; 29(7 Suppl):S99–106. [PubMed: 11445742]
3. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med. 2003; 348:138–150. [PubMed: 12519925]
4. Carre JE, Orban JC, Re L, et al. Survival in critical illness is associated with early activation of mitochondrial biogenesis. Am J Respir Crit Care Med. 2010; 182:745–751. [PubMed: 20538956]
5. Crouser ED. Mitochondrial dysfunction in septic shock and multiple organ dysfunction syndrome. Mitochondrion. 2004; 4:729–741. [PubMed: 16120428]
6. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. Lancet. 2002; 360:219–223. [PubMed: 12133657]
7. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. Jama. 1995; 274:639–644. [PubMed: 7637145]
8. Belikova I, Lukaszewicz AC, Ass VF, et al. Oxygen consumption of human peripheral blood mononuclear cells in severe human sepsis. Crit Care Med. 2007; 35:2702–2708. [PubMed: 18074472]
9. Calvano SE, Xiao W, Richards DR, et al. A network-based analysis of systemic inflammation in humans. Nature. 2005; 437:1032–1037. [PubMed: 16136080]
10. Zapelini PH, Rezin GT, Cardoso MR, et al. Antioxidant treatment reverses mitochondrial dysfunction in a sepsis animal model. Mitochondrion. 2008; 8:211–218. [PubMed: 18417427]
11. Japiassu AM, Santiago APSA, d'Avila JCP, et al. Bioenergetic failure of human peripheral blood monocytes in septic shock patients is mediated by reduced F1Fo ATP synthase activity. Crit Care Med. 2011 xxxxx.
12. Brealey D, Karyampudi S, Jacques TS, et al. Mitochondrial dysfunction in a long-term rodent model of sepsis and organ failure. Am J Physiol Regul Integr Comp Physiol. 2004; 286:R491–R497. [PubMed: 14604843]
13. Crouser ED, Julian MW, Blaho DV, Pfeiffer DR. Endotoxin-induced mitochondrial damage correlates with impaired respiratory activity. Crit Care Med. 2002; 30:276–284. [PubMed: 11889292]
14. Sjovall F, Morota S, Hansson MJ, et al. Temporal increase of platelet mitochondrial respiration is negatively associated with clinical outcome in patients with sepsis. Crit Care. 2010; 14:R214. [PubMed: 21106065]
15. Huang LJ, Hsu C, Tsai TN, et al. Suppression of mitochondrial ATPase inhibitor protein (IF1) in the liver of late septic rats. Biochim Biophys Acta. 2007; 1767:888–896. [PubMed: 17490602]

16. Singer M, De Santis V, Vitale D, Jeffcoate W. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet. 2004; 364:545–548. [PubMed: 15302200]

17. Wallace DC. Mitochondrial diseases in man and mouse. Science. 1999; 283:1482–1488. [PubMed: 10066162]