Commentary Article

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Sepsis, Nutrition and Mitochondrial Energetics

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Abstract

The hypermetabolic response during acute inflammation in sepsis is rapidly replaced by a hypometabolic state as the organism struggles to balance severe stress responses of resistance and tolerance. Conceptually, therapeutic targeting of mitochondrial bioenergetic pathways may resolve immune and multi-organ failure and improve survival. Current pre-clinical data are consistent with the postulate that dysfunction of the mitochondrial pyruvate dehydrogenase complex drives many of the immuno-metabolic complications of severe infection. Targeting this pathway resolves epigenetic, bioenergetic, nutritional, and oxidation/reduction dysregulation in cells and organs and provides survival benefit during the acute immune response.

Keywords: Sepsis; Septic shock; Bioenergetics; Pyruvate dehydrogenase complex

Commentary

Lethal and near-lethal sepsis promotes a starvation-like state that metabolically and energetically resembles hibernation [1]. The starvation state emerges when the energy-expensive sepsis phase that mounts resistance makes a tradeoff to a hypo-metabolic form of disease or sickness tolerance [2]. An infected organism's ability to successfully balance resistance and tolerance is a universal survival strategy of all life histories [3]. Uncontrolled resistance to infection induces septic shock, and inflexible tolerance enables the hypo-metabolic starvation-like state associated with failure of injured organs to regenerate [4]. At present, there is no molecular-based treatment for sepsis.

Our concept is that sepsis separates energy demand and supply but can be therapeutically-targeted by stimulating mitochondrial bioenergetics. The Pyruvate Dehydrogenase Complex (PDC) is such a target. This nuclear-encoded mitochondrial megacomplex catalyzes the rate-limiting step in aerobic glucose oxidation by irreversibly converting glycolysis-derived pyruvate to Acetyl Coenzyme A (acetyl CoA). In turn, acetyl CoA feeds the Tri Carboxylic Acid (TCA) cycle that generates the "reducing equivalents" (NADH and FADH2) utilized by the mitochondrial respiratory chain to convert respired oxygen to water and to synthesize the energy-rich molecule Adenosine Triphosphate (ATP) by a process called Oxidative Phosphorylation (OXPHOS). In a murine model of severe sepsis, we found that PDC is reversibly phosphorylated, and thereby inhibited, by pathological up-regulation of Pyruvate Dehydrogenase Kinase (PDK). A decrease in the level of acetyl CoA not only limits oxidative phosphorylation but also disrupts cytosolic protein acetylation and thus epigenetically reprograms nuclear chromatin.

The second example of energy tradeoffs detrimental to the infected host is a disrupted (broken) TCA cycle [5]. One break occurs when the TCA cycle enzyme aconitase diverts citrate-derived cis-aconitate to itaconate. Itaconate broadly supports immune tolerance in mononuclear phagocytes and perhaps other cell types expressing danger sensors. A second TCA separation occurs at Succinate Dehydrogenase (SDH), an enzyme of both the TCA cycle and the respiratory chain, the latter known as Complex II. The net outcome of TCA cycle disruption is a fall in ATP levels and a marked reduction in anabolic support of biomass production. If the sepsis-induced breach in energetics remains inflexible, death ensues from immune suppression and irreversible organ failure.

Why then do some sepsis victims live and so many do not? A hint is that targeting PDK with the prototypic inhibitor Di Chloro Acetate (DCA) can dephosphorylate, and thus reactivate, PDC. By the same mechanism, the drug reverses diapause (hibernation) in insects [6]. We discovered that DCA treatment of mice in septic shock restores mitochondrial oxidative bioenergetics in monocytes and splenocytes, promotes vascular, immune and organ homeostasis, accelerates bacterial clearance and markedly increases survival [7]. More recently, we found that DCA stimulates appetite and limits weight loss in septic mice and rebalances mitochondria fusion and fission in septic mouse macrophages. Together, these studies strongly suggest that the life-threatening separation of energy demand and supply and its starvation sequelae in septic mice are reversible.

Given that DCA's mode of action is presumed to be due exclusively to systemic reactivation of PDC by inhibiting PDK-mediated phosphorylation, the consequences to the host's nutritional status beyond mitochondrial OXPHOS are multiple. First, restoration of liver function preserved the organ's biosynthetic machinery, including reduction in elevated transaminitis and increased hepatic glucose output and circulating glucose levels, which are reduced in experimental and human sepsis [8]. Second, PDC activation repaired TCA cycle

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function, reducing itaconate concentrations and normalizing levels of the TCA cycle intermediates fumarate and malate, molecules that interact with the urea cycle. Third, in hepatocytes from septic animals, increased PDC activity led to reduction in Reactive Oxygen Species (ROS) formation and to repletion of intracellular redox components cystathionine, cysteine, glycine, hypotaurine, taurine and glutathione and, hence, to reduced tissue redox stress. Fourth, PDC reactivation in hepatocytes from septic mice reduced triglyceride and lipid droplet accumulation, rebalanced levels of phospholipid species and fatty acid acyl carnitine derivatives.

In conclusion, reactivation of PDC elicits diver's downstream metabolic effects of nutritional and, thus, survival value to a host defending against life-threatening infection. The possible effective translation of these preclinical findings to humans represents an exciting and novel mechanistically-oriented therapeutic approach to sepsis, the most common cause of in-hospital mortality, treatment of which has been limited for generations to only supportive care.

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