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REVIEW

Sepsis, pyruvate, and mitochondria energy supply chain shortage

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Abstract

Balancing high energy-consuming *danger resistance* and low energy supply of *disease tolerance* is a universal survival principle that often fails during sepsis. Our research supports the concept that sepsis phosphorylates and deactivates mitochondrial pyruvate dehydrogenase complex control over the tricarboxylic cycle and the electron transport chain. StimulatIng mitochondrial energetics in septic mice and human sepsis cell models can be achieved by inhibiting pyruvate dehydrogenase kinases with the pyruvate structural analog dichloroacetate. Stimulating the pyruvate dehydrogenase complex by dichloroacetate reverses a disruption in the tricarboxylic cycle that induces itaconate, a key mediator of the disease tolerance pathway. Dichloroacetate treatment increases mitochondrial respiration and ATP synthesis, decreases oxidant stress, overcomes metabolic paralysis, regenerates tissue, organ, and innate and adaptive immune cells, and doubles the survival rate in a murine model of sepsis.

KEYWORDS
dichloroacetate, energy shifts, evolution, immunometabolism, inflammation, itaconate, pyruvate, redox

1 | INTRODUCTION

One reason for the dearth of molecular targeting drugs for sepsis is that a limited understanding of the biochemical mechanisms responsible for life-threatening organ and immune failure hampers scientists' ability to design rational sepsis treatments. The severe stress of sepsis invokes a conserved biochemical response designed to survive the threat, limit destruction, and restore homeostasis. The high energy needs of *danger resistance* restrains microbial invasion and replication, in part by increasing oxidant stress. To limit consequent oxidant injury, *disease tolerance* reduces energy requirements endeavoring to restore homeostasis. The clinically obscure immunometabolic paralysis of sepsis precludes restoring energy homeostasis and portends chronic disease and/or death. In designing molecular interventions, a critical unanswered question is whether sepsis survival follows evolution's universal survival route of balancing *resistance* to life-threatening infection with *tolerance* to a potentially lethal systemic inflammatory disease syndrome.[1,2]

2 | THE MITOCHONDRIAL ENERGY DEMAND AND SUPPLY CHAIN SEPARATES DURING SEPSIS

The progression from an organism's initial high energy consuming resistance to an invading pathogen to a low energy state of disease

ABBREVIATIONS: DCA, dichloroacetate, PDK inhibitor; PDC, pyruvate dehydrogenase complex; PDK, pyruvate dehydrogenase kinase; PDP, pyruvate dehydrogenase phosphatase; SIRT, Sirtuin; TCA, mitochondrial tricarboxylic cycle (Krebs cycle).

tolerance is a universal survival strategy preserved throughout evolution.[5] Examples of this biochemical opposition are the hyperarousal of acute stress and the torpor of hibernation and estivation.[6–9] A transition (trade-off) from energy consuming *danger resistance* to a hostile environment to a low energy state of *disease tolerance* also occurs during sepsis where pathogen resistance processes are balanced by mechanisms to limit collateral tissue damage.[4] Sepsis, however, fails the host's resistance-to-tolerance shift in 2 ways.[1,10,11] First, during resistance, excessive inflammation activation generates reactive oxygen species inducing oxidative stress within the microvasculature that can precipitate septic shock.[12,13] Second, the low-energy supply and antioxidative disease tolerance compromise immune and vital organ cells' abilities to promote growth and reverse immunometabolic paralysis.[14] Figure 1 is a simplified scheme of the infection-induced trade-off between the high energy resistance and low energy disease tolerance phenotypes that is imbedded in our previous understanding of proinflammatory and anti-inflammatory responses in sepsis.

3 | THE TEMPORAL REPROGRAMMING OF MITOCHONDRIAL ENERGY DURING SEPSIS IS ILL DEFINED

The rapid shift of infection resistance to disease tolerance is often over within 4–8 h after sepsis disseminates its life-threatening inflammatory shock syndrome.[8,10,15–18] After that, the clinically obscure switch from a high to a low energy environment can last for days, weeks, or even years.[19–21] Figure 1 depicts the concept of an energy trade-off with glycolysis-derived pyruvate poised to inform the switch between resistance and tolerance. As reviewed here, the pyruvate dehydrogenase complex (PDC) and its time course of reversible phosphorylation during resistance and tolerance are critical to understanding sepsis disease syndromes and identifying targeted treatments.

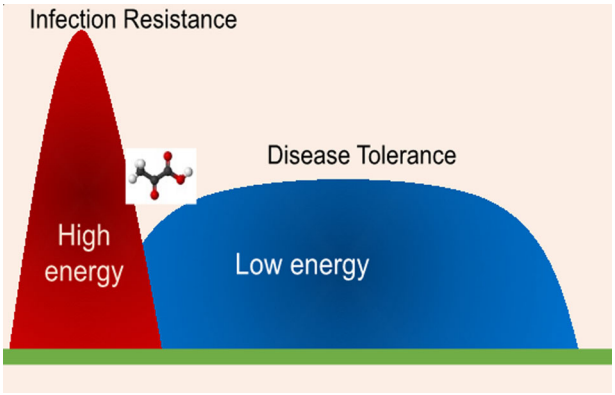

FIGURE 1 Sepsis energy trade-off. As a universal principle of survival, acute stress responses balance energy demands necessary to resist physical illness and injury with energy conservation to tolerate and survive. Molecular events associated with resistance and tolerance overlap, but 1 of the 2 usually dominates and both are life threatening. The severe stress of sepsis often leads to an energy imbalance, immunometabolic "paralysis" and energy depletion that is unresolved. Many sepsis patients experience a mechanistically obscure and persistent low-grade inflammation, unrelenting immune suppression, and chronic disability with continued increases in mortality. Our studies in animal sepsis models, ex vivo analyses of cells from septic animals, and in vitro human cell sepsis models suggest that pyruvate is poised at the intersection of pathways that provide key energy metabolites including carbohydrates, fatty acids, and acetyl CoA. Further understanding pyruvate metabolism may enlighten therapeutic options for improving sepsis outcomes.

4 | SEPSIS REQUIRES GLUCOSE, FATTY ACID, AND AMINO ACIDS AS ENERGY SUBSTRATES

The energy demands of infection resistance during sepsis are hypermetabolic and energy expensive, but the transition to a hypometabolic and low energy supply state of disease tolerance rapidly dominates.[8,22–25] PDC control over glucose oxidation supports the TCA cycle properties of anabolism and catabolism and ATP synthesis by converting pyruvate to acetyl CoA.[26,27] Acyl carnitine derivatives of fatty acids and various amino acids, for example, branched-chain leucine, isoleucine, and valine, also support TCA cycle energetics.[28–33] For example, increases in acylcarnitine long- and short-chain fatty acids and decreases in central carbon sources typify sepsis reprogramming to disease tolerance in humans, nonhuman primates, and mice.[34,35] Low energy disease tolerance may progress to advanced starvation with a broad decrease in amino acids and disruption of protein synthesis supported by mammalian target of rapamycin.[21,36] To survive sepsis, fuel sources must remain flexible to restore homeostasis that requires the PDC axis.

5 | PDC DEACTIVATION CREATES AN ENERGY SUPPLY CHAIN SHORTAGE DURING SEPSIS

After entering mitochondrial transporters, pyruvate is irreversibly oxidized by PDC to acetyl CoA[37] and as such, PDC acts as an energy homeostat bridging glycolysis to energy production. PDC metabolic control over the TCA cycle and oxygen reduction to drive ATP synthesis requires decarboxylation of glycolysis-derived carbons. Sepsis, however, skews carbohydrate metabolism away from mitochondrial oxidation and promotes the cytoplasmic reduction of pyruvate to lactate.[38] Lactate represses innate and adaptive immunity.[39] We noted that pyruvate dehydrogenase kinase 1 (PDK1) expression inactivated PDC, creating an energy supply chain decrease in immune and vital organ cells during sepsis.[3] Conversely, PDK1 inhibition reversed the energy supply chain shortage of sepsis by restoring PDC activity to convert pyruvate to acetyl-CoA.[40] PDK4 is another more broadly expressed isoform that inactivates PDC to cause cardiomyocyte weakness and may underlie multiorgan failure.[41] Changes in pyruvate dehydrogenase phosphatase (PDP) also may influence PDC activity, furthering an impact on energy balance.[42]

The highly conserved metabolism of the PDC (Figure 2) supports the therapeutic potential of targeting the PDK/PDC/PDP energy axis

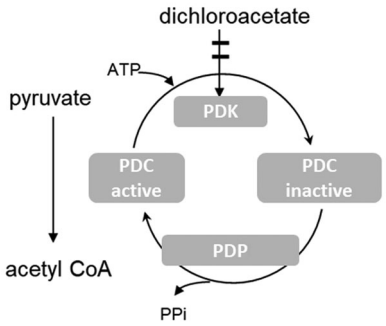

FIGURE 2 Regulation of PDC activity. Rapid posttranslational regulation of PDC is affected by its reversible phosphorylation by tissue selective actions of PDC kinases (PDK) and phosphatases (PDP). DCA inhibits PDK and activates PDC. During aerobic respiration, pyruvate is decarboxylated by PDC and produces acetyl-CoA

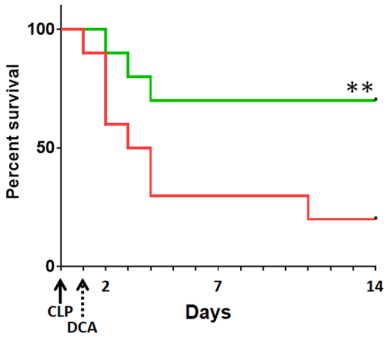

FIGURE 3 DCA increases survival in a mouse model of sepsis. To assess the effect of DCA on survival, we used a mouse model of sepsis (CLP) as previously described.[3] At 24 h after CLP, mice were treated with a single intraperitoneal dose of 25 mg/kg of DCA (CLP+DCA) or a vehicle control (CLP + vehicle). Kaplan–Maier survival curve shows that DCA (CLP + DCA) significantly improved 14-day survival when compared with vehicle treatment (CLP + vehicle) in the absence of antibiotics. $N = 20$ mice/cohort; Log-rank (Mantel–Cox) test, $^{**}p < 0.01$

during sepsis. PDC is a 9 million Dalton mega-complex with 3 major enzymatic components, E1, E2, and E3.[43] Pyruvate and 2 other oxo-ketoacids use a decarboxylation step and a lipoic trans-acetylase to generate multifunctional acetyl CoA.[44] This conserved pyruvate-dependent pathway balances anabolism, required for pathogen resistance, with catabolism, necessary for disease tolerance. Biochemical mediators directing mitochondrial energy demand and supply during sepsis are TLRs, NFκB p65 transcription activator and RelB repressor, transcription permissive euchromatin and restrictive heterochromatin by NAD-dependent Sirtuins (SIRTs), anabolic and catabolic metabolic shifts, and PDK regulation of PDC.

6 | DICHLOROACETATE RESETS THE PDC ENERGY HOMEOSTAT TOWARD SURVIVAL

Dichloroacetate (DCA) is the prototypic drug to inhibit PDK. The resulting PDH activity increases the flux of pyruvate into the mitochondria and promotes glucose oxidation over glycolysis.[43,45] In mouse model of sepsis, we found that DCA treatment reverses cardiovascular shock, decreases hepatocellular injury, hyperlactatemia, and hyperglycemia, reverses immune-metabolic paralysis, improves clearance of bacteria without antibiotics, and as shown in Figure 3, significantly increases sepsis survival.[3] We also observed that DCA treatment before sepsis onset (0 h) or during the oxidative stress phase following induction of sepsis (6 h) also significantly increases survival (data not shown). To our knowledge, DCA is the only investigational drug currently in clinical testing that normalizes oxidative stress during infection resistance and reverses low energy disease tolerance while increasingoxidation of glucose and fatty acids.

7 | DCA RESETS METABOLISM INCELL AND MOUSE MODELS OF SEPSIS

To gain insight into the immunometabolism of human sepsis, we used a cell model where we had previously identified transcription and epigenetic outcomes of the sepsis response (reviewed in 1). Human promonocytes, THP-1 tissue culture cells, were treated with bacterial LPS (endotoxin) for various times with or without DCA.[10] Using unbiased metabolomics, Figure 4 summarizes this study identifying metabolites decreased (green) during the acute stress of inflammation and the overall effect of DCA on mitigating the stress responses by increasing (red) intermediary metabolism including amino acids, peptides, carbohydrates, TCA cycle, lipids, nucleotides, cofactors and vitamins, amino acids, vitamins, nucleotides, and xenobiotics. Many of the mitochondrial metabolic effects of DCA treatment depicted occur in septic mice, isolated mouse hepatocytes, human primary monocyte models, and severe acute inflammation.[11,22,27,28] Rigorous research implicates low energy supply in human and nonhuman primate sepsis; however, these studies did not assess the PDK/PDC/PDP pathway.[15,35,46]

The TCA cycle is disrupted at isocitrate dehydrogenaseand succinate dehydrogenase in acutely inflamed monocytes and hepatocytes isolated from septic mice.[1,47] DCA treatment restores the TCA cycle in endotoxin-treated human monocytes in vitro and in hepatocytes isolated from septic mice, restores anabolism and ATP synthesis, and regenerates immune and organ cell fate and function.[40,47] As a novel pathway to maintain energy equilibrium, elevated levels of the TCA cycle catabolic and antioxidant mediator of tolerance, itaconate is decreased in DCA-treated human monocyte cell models[47] and in isolated hepatocytes following DCA treatment of septic mice.[10,40]

DCA also attenuates several host responses that are characteristic of disease tolerance, including anorexia, weight loss, and compromised whole body respiration in septic mice.[40] Indices of oxidant stress reverse in DCA-treated human monocytes and in macrophages and hepatocytes from septic mice.[40] Together, these findings support primary and/or indirect secondary effects of DCA across the septic organism.[48] Since DCA normalizes corticosteroid levels in the liver

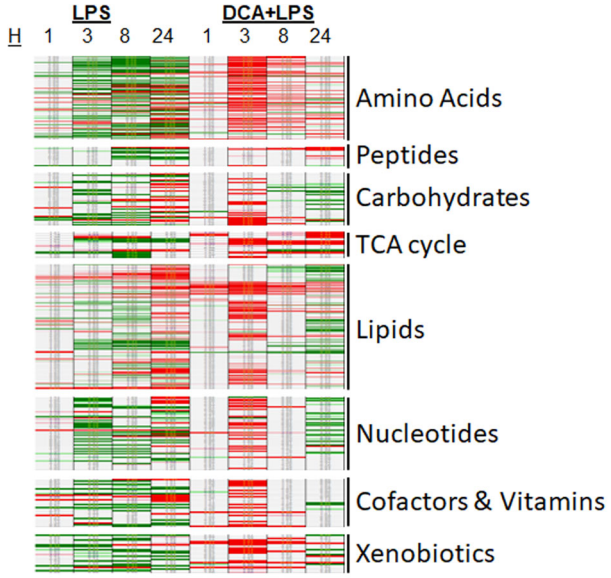

FIGURE 4 PDC activation broadly alters intermediary metabolism in a cell culture model of sepsis. Using endotoxin (*E. coli* 0111:B4) treatment (1 μg/ml)' , THP-1 cell-line monocytes were pretreated with vehicle (untreated) or with DCA for 30 min and subsequently stimulated without or with LPS for the indicated time(s). For each time point, fold change differences of intracellular metabolites of LPS relative to untreated cells (LPS) and DCA + LPS relative to LPS stimulated cells (DCA + LPS) are shown. Green (decrease) boxes indicate significant difference ($p \leq 0.05$) between the groups shown; metabolite ratio of <1.00. Light green boxes indicate narrowly missed statistical cutoff for significance $0.05 < p < 0.10$; metabolite ratio of <1.00. Red (increase) boxes indicate significant difference ($p \leq 0.05$) between the groups shown; metabolite ratio of ≥1.00. Pink boxes indicate narrowly missed statistical cutoff for significance $0.05 < p < 0.10$; metabolite ratio of ≥1.00. $N = 5$

and plasma of septic mice, hypothalamic reprogramming may promote survival.

8 | THE PRECISE MOLECULAR MECHANISMS UNDERLYING ENERGY IMBALANCE DURING SEPSIS ARE UNCLEAR

Despite broad-based corrections in immunity, multiorgan failure, and inflammatory shock, a precise understanding of how DCA broadly resets PDC subcomponents is missing. Recent evidence supports oxidative crosstalk between PDC complex 3 E3 and TCA cycle aconitase 2 that disrupts TCA cycle before isocitrate and synthesizing itaconate.[49] As another redox response during sepsis, we reported that specific cysteine thiols on NAD-dependent SIRTs 2 and 6 inhibit glycolysis.[11,40,50,51] Undoubtedly, there is a remarkable breadth in sepsis-induced responses and our observations implicate DCA resets the anabolism and catabolism energy imbalance throughout the septic host, not just innate immune cells. It is important to identify these changes in sepsis endotypes/phenotypes and does not preclude potential targets other than PDC as mediators of survival with DCA treatment.[52,53] Our present working theory is that investigating the cysteine thiol redox axis may identify time-sensitive biomarkers of the mitochondria energy supply chain shortage during sepsis.[51,54]

9 | "NOTHING IN BIOLOGY MAKES SENSE EXCEPT IN THE LIGHT OF EVOLUTION." THEODOSIUS DOBZHANSKY

The beginnings of life's origin perhaps used pyruvate, heavy metals, and glyoxylate as catalysts for the TCA cycle development and anaerobic energetics.[55] Life then evolved fixed and moving structures from CO_2 using 5 energy metabolic hubs[56] that included pyruvate, acetate, oxaloacetate, succinate, and alpha-ketoglutarate. Early survival needed these chemicals without or with ATP to implement the universal survival principle of *resistance and tolerance* to environmental stressors.[57–59] Added to survival were the universal principles of *growth and replication*, which enabled successful competition for limited resources.

Mitochondria emerged after proteobacteria, and archaea integrated.[60–62] Pyruvate directed anaerobic energetics, while acetate and methyl chemistry supported genetic stability and inheritance.[58] About 3 billion years ago, cyanobacteria used CO_2 and photosynthesis to initiate the "Great Oxygenation Era,"[63–65] which lasted over a billion years. During that era, atmospheric oxygen rose to over 30% before decreasing gradually to[66] the present atmospheric oxygen level of 21% (v/v), which enabled human evolution. Anaerobic and aerobic energetics became part of the universal high to low energy trade-off during stress, in whichpyruvate metabolism helped maintain the flexible energy economy of supply and demand now needed for surviving sepsis.[6,42,57,67,68] A nexus of antioxidant control from evolution emerged during elevation of atmospheric oxygen when many life forms perished.[66] Notably and emphasizing the PDK/PDC nexus, a recent study of *Drosophila* diapause showed that DCA arouses the pupal hibernation-like hypometabolic state that sustains pyruvate dehydrogenase kinase deactivation of PDC.[69,70] PDC also contributes to arousal from hypometabolic hibernation.[6,69,71,72]

The evidence for pyruvate metabolism and its control over energy supply/demand dynamics and redox poise is compelling as an emergent concept for understanding the universal survival route of resistance and tolerance during sepsis.

Important unanswered questions include:

1. Are there time and organ/tissue-specific effects of PDC on infection resistance and disease tolerance during sepsis?
2. Can DCA promote homeostasis and survival in human sepsis?
3. Is there a cysteine thiol redox code underlying sepsis?
4. Does PDC crosstalk with mitochondrial alpha keto-glutarate dehydrogenase, branched-chain amino acid dehydrogenase, and dihydroorotate dehydrogenase?
5. Does the DCA survival mechanism correct defects in protein translation?

6. How do sepsis endotypes affect PDC control over energy supply and demand?

10 | CONCLUSION

Life-threatening sepsis disrupts PDC control over the mitochondrial energy supply chain in immune cells and vital organ cells in sepsis models. DCA targets sepsis-induced defects in mitochondrial energy supply and demand by restoring PDC support of the TCA cycle and ATP synthesis, thereby promoting homeostasis and survival.

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AUTHORSHIP

C. E. M., X. Z., M. A. Q., B. K. Y., P. W. S., and V. V. conceived, designed, and analyzed/interpreted the data. M. Z. and D. L. conducted experiments and prepared results. C. E. M. and B.K.Y primarily wrote the manuscript.

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