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Overcoming the Warburg Effect: Is it the key to survival in sepsis?

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ABSTRACT

Sepsis is a leading cause of mortality in the U.S. and Europe. Sepsis and septic shock are the results of severe metabolic abnormalities following infection. Aerobic glycolysis (the Warburg Effect) is as much a hallmark of sepsis as it is of cancer. Warburg observed that cancer cells generated energy through glycolysis (generation of ATP through degradation of glucose, usually associated with anaerobic conditions) rather than through oxidative phosphorylation (generation of ATP through the mitochondrial inner membrane via the tricarboxylic acid cycle, usually associated with aerobic conditions). Although the initial pathways of cancer and sepsis may be different, the mechanisms which allow aerobic glycolysis to occur, even in the presence of oxygen, are similar. This review provides some evidence that reversing these steps reverses the Warburg Effect in model systems and some pathological consequences of this effect. Therefore, this implies that these steps might be modifiable in sepsis to reverse the Warburg Effect and possibly lead to better outcomes.

Contents

Abbreviations: PDC, pyruvate dehydrogenase complex; TCA, tricarboxylic acid cycle; PKM2, pyruvate dehydrogenase kinase 2; HMGB1, high mobility group box 1 protein; LPS, lipopolysaccharide; SDH, succinate dehydrogenase; ETC, electron transport chain; PHD, prolyl hydroxylase; HIF-1α, hypoxia-induced transcription factor alpha; EIF2AK2, eukaryotic translation initiation factor 2-alpha kinase 2; ROS, reactive oxygen species.

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1. Introduction

Sepsis is a leading cause of mortality in the U.S. and Europe [1,2]. In the U.S., there are approximately 750,000 cases of severe sepsis and septic shock annually, leading to over 200,000 deaths [1]. The dramatic worldwide increase in infections caused by multi-drug resistant bacteria, especially gram-negative bacteria, exacerbates this already serious condition [3]. Early use of antibiotics and correction of physiologic abnormalities is the usual course of treatment. Respiration is almost always stabilized by administering oxygen, and tracheal intubation and mechanical ventilation are often required to keep a patent airway and adequate alveolar ventilation. Vasopressors are administered for hypotension. Hypovolemia is treated by fluid resuscitation, with crystalloids or human serum albumin. A number of pharmaceutical products have been tested and all did not show efficacy in phase III or follow up clinical trials. More recently, Marik et al. reported successful treatment of sepsis by the addition of a combination of a steroid, vitamin C and thiamine to established sepsis management [4].

Sepsis and septic shock are the results of severe metabolic abnormalities following infection. Sepsis begins with a hyper-inflammatory period where macrophages, monocytes, T cells, and neutrophils are activated and recruited to various organs. This is followed by hypo-inflammatory responses characterized by metabolic deterioration that may lead to death [5]. One of the characteristics of sepsis and septic shock is an increase in serum lactate. These increased lactate levels at the time of hospital admission are a strong indicator of outcome, irrespective of treatment regimens in the ICU [6-8]. Research efforts to explain the cause of septic shock has focused on the interaction among low oxygen delivery to tissues, glycolysis versus oxidative phosphorylation in cells from affected organs, and damage from reactive oxygen and nitrogen species.

Hallmark symptoms of sepsis are decreased availability of oxygen to tissues secondary to low arterial oxygen levels, decreased hemoglobin levels, and/or hypoperfusion thereby inhibiting ATP production via the TCA cycle [9]. Explaining hypoxia and reduced oxygen extraction in sepsis is complicated and has always been a topic of controversy in clinical medicine. As a result, the role of mitochondrial dysfunction in the induction of cellular hypoxia has become a major focus in sepsis research. Several mechanisms of mitochondrial dysfunction due to sepsis have been proposed including: 1) damage to the inner mitochondrial membrane by ROS production resulting in a proton leak; 2) PDC instability; 3) inhibition of key TCA enzymes; 4) inhibition of mitochondrial enzyme complexes; and/or 5) general damage by ROS (reviewed by [10]). Adding to the complexity is the biphasic properties of sepsis. Early sepsis (<48 h) is characterized by a strong pro-inflammatory response with increased metabolic activity and mitochondrial function while late sepsis (>48 h) is virtually the exact opposite with prevalent immunosuppression with impaired energy production possibly due to mitochondrial dysfunction [11].

2. Sepsis and the Warburg Effect

Otto Warburg observed that cancer cells generated energy through glycolysis (generation of ATP through degradation of glucose, usually associated with anaerobic conditions) rather than through oxidative phosphorylation (generation of ATP through the mitochondrial inner membrane via the tricarboxylic acid cycle, usually associated with aerobic conditions) [12]. Warburg postulated that this was the key distinguishing element between cancer and non-cancer cells [13]. He further postulated that this effect was the result of irreversible inactivation of mitochondria. Current belief is that mitochondrial inactivation rarely occurs [14]. Today, we know that the aerobic switch from oxidative phosphorylation to glycolysis, still known as the Warburg Effect, is biochemically complex and is controlled by many factors in tissue metabolism.

The Warburg Effect has been best studied in cancer cells [15,16], but it is as much a hallmark of sepsis as it is of cancer. Although the initial pathways may be different, the mechanisms which allow glycolysis to occur, even in the presence of oxygen, are similar [17-19]. One of the first lessons learned about the pro-inflammatory response in sepsis was that hypoxia, known to trigger glycolysis in inflammation and in cancer, may contribute to this effect. However, in these pathologies, glycolysis continues even in the presence of adequate delivery of oxygen to the affected tissues [20,21]. More importantly, current research demonstrates that pharmacologic reversal of the Warburg Effect restores oxidative phosphorylation when oxygen is present.

3. Biochemical changes

The biochemical events that lead to the utilization of glycolysis even in the presence of adequate oxygen in both tumor cells and septic tissues are multiple [20]. Our goal here is not to list all of the biochemical pathways that are potential targets for reversing the Warburg Effect in sepsis. Rather, the focus is to highlight two of the many possible changes leading up to aerobic glycolysis in sepsis and to suggest that these could become the targets of research into therapeutics for sepsis, the therapy of which is crying out for new approaches.

The first key biochemical step regarding the Warburg Effect in sepsis is the entry of pyruvate into the mitochondria. Pyruvate is oxidatively decarboxylated to acetyl CoA which can be used in the tricarboxylic acid cycle. This step is facilitated by a complex enzyme, the pyruvate dehydrogenase complex (PDC). Inhibition of PDC allows the 2 pyruvate molecules derived from one glucose molecule in the cytoplasm to produce 2 molecules of ATP via glycolysis. When PDC functions normally, it results in the formation of 36 molecules of ATP for every molecule of glucose oxidized in the TCA cycle. The last step in glycolysis before the entry of pyruvate into the mitochondria for oxidative phosphorylation is the catalytic conversion of phosphoenolpyruvate to pyruvate. This reaction is influenced by a number of enzymes in the PDC, some of which share the same catalytic activity and are called pyruvate dehydrogenase kinases. One of these pyruvate dehydrogenase kinases (PKM2) inactivates PDC and the creation of Acetyl CoA depending on its phosphorylation status. Additionally, regulating the entry of PKM2 into the nucleus results in the transcription of genes whose expression inhibits oxidative phosphorylation [22]. The phosphorylation levels of PKM2 are also regulated by two PDC phosphatases, whose activity can increase the transfer of pyruvate to the mitochondria for oxidative phosphorylation. Stimulation of the sepsis pathways in HepG2 hepatocarcinoma cells leads to both a stimulation of PKM2 mRNA and a decrease of PDC phosphatase mRNA. Both these effects inhibit the use of pyruvate in the tricarboxylic acid cycle keeping pyruvate in the cytosol. Pyruvate could then be reduced to lactate, even in the presence of oxygen [8].

The second biochemical pathway with respect to the Warburg Effect in sepsis is the accumulation of succinate in inflammation and the notion of reversing this accumulation as a therapeutic possibility. In inflammatory states, succinate accumulates via 2 major pathways and one minor one. Succinate accumulation is important regarding the persistence of glycolysis even in normoxic conditions. Succinate is a normal intermediate in the TCA cycle, being formed from alpha ketoglutarate via alpha ketoglutarate dehydrogenase and succinyl-CoA synthetase. It is subsequently oxidized to fumarate by succinate dehydrogenase (SDH). SDH is both a TCA cycle enzyme and an integral part of the mitochondrial electron transport chain (ETC). In normal respiration, the TCA cycle intermediates are maintained at a constant level for respiration. However, when other metabolic demands are made on the TCA cycle intermediates, they must be replenished via what are termed anaplerotic reactions. One such reaction is catalyzed by glutamate dehydrogenase which oxidizes glutamate to alpha ketoglutarate, the direct precursor of succinate in the TCA cycle. When bone marrow derived macrophages are treated with LPS, the concentration of succinate is increased 30-fold