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# Sepsis Immunometabolism: From Defining Sepsis to Understanding How Energy Production Affects Immune Response

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**Objectives:** This review will examine current definitions and trends in sepsis management as well pathophysiologic mechanisms in animal and ex vivo studies that correlate decreased energy production with deranged inflammatory response during the septic process.

**Data Sources:** The latest articles in the literature that focus on the role of immunometabolism and associated mechanisms in sepsis were selected.

**Study Selection:** The most relevant, original articles were included in the review.

**Data Extraction:** All pertinent data for sepsis definitions as well as changes in immunometabolic pathways during the septic process was reviewed and assessed for inclusion in this article.

**Data Synthesis:** Sepsis is a major cause of multiple organ dysfunction. It is the principal cause of death resulting from infection and one of the most expensive conditions treated in the United States. Despite current efforts to accurately define sepsis, novel treatments and highly trained providers, mortality rates for sepsis remain high, prompting a need for further investigation of underlying immunometabolic mechanisms to identify potential treatment targets. The definition of sepsis has shifted and changed in the past few decades due to poorly defined criteria, as well as unclear guidelines for providers with regards to management of severe sepsis and septic shock. The early identification of patients with a systemic inflammatory response that will progress to septic shock is critical since recent traditional therapeutic approaches, such as early goal-directed therapy, IV immunoglobulin, and anti–tumor necrosis factor-α antibodies have failed.

**Conclusions:** There are no effective anti-sepsis drug therapies due to complex inflammatory and metabolic interactions. Further studies regarding the interface between innate immunity and metabolism should be investigated to effectively address septic patient mortality rates.

**Key Words:** energy production; immune response; inflammation; metabolism; sepsis

Sepsis continues to be a major cause of morbidity and mortality despite the discovery and development of antibiotics and the advancement of our understanding of septic mechanisms over the past century. Globally, there are over 30 million cases of sepsis yearly and an estimated 5 million fatalities that can be attributed to sepsis (1). Sepsis has been identified in 35% of all hospital patient deaths and it is the most expensive condition treated in U.S. hospitals, costing nearly 24 billion dollars annually (2–5).

The term sepsis has been used for over 2000 years (6). The American College of Chest Physicians/Society of Critical Care Medicine met in 1991 to develop definitions for the body's inflammatory response to infection, sepsis, and its sequelae (7). This consensus conference, now commonly known as Sepsis-1, coined the term systemic inflammatory response syndrome (SIRS) which describes an inflammatory state that can arise from various insults including infection, trauma, burns, or pancreatitis (7).

In 2001, the Sepsis-1 definition was reviewed and revised because experts in the field recognized the limitations of SIRS and wanted to expand clinical criteria for sepsis. The Sepsis-2 definitions identified infection as "a pathologic process caused by invasion of a normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic micro-organisms" (8). Until

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this point, there were no pediatric definitions for SIRS or sepsis in children, but in 2002, an international pediatric consensus adapted the adult criteria to the pediatric population and included appropriate physiologic cutoffs (9).

After several years of advancement in the clinical and scientific understanding of sepsis, a third international consensus in 2014 (Sepsis-3) was held to recommend new sepsis criteria, recognizing that sepsis is a complex entity and has both inflammatory and anti-inflammatory elements. Sepsis-3 redefined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection" (10). Importantly, this consensus added organ dysfunction to the definition of sepsis and recommended that assessment of organ dysfunction use one of two different scoring methods: the Sequential Organ Failure Assessment (SOFA) for inpatient settings and the quick SOFA (qSOFA) for emergency/outpatient settings. Although SIRS failed to distinguish between the body's normal inflammatory response to infection or injury and a dysregulated response, qSOFA and SOFA improved the ability to identify sepsis by adding components of organ dysfunction (10–13).

## WHY SEPSIS TREATMENTS NEED FURTHER INVESTIGATION

Despite the evolution of the definition of sepsis over time and improvements in sepsis care, sepsis mortality rates remain high and can reach 25% (1–5, 13). One protocol for patients presenting to the emergency department with septic shock, first introduced in 2001, is early goal-directed therapy (EGDT). It was developed based on the success of goal-directed care that patients in the ICU receive for sepsis and septic shock (14). This 6-hour protocol consists of early recognition of sepsis, with aggressive management of central venous pressure, mean arterial pressure, and hematocrit (14). Although this single study reported reduced mortality rates, in a large meta-analysis EGDT failed to demonstrate overall benefit with regard to mortality, compared with usual care of patients with septic shock (15). Additionally, it also showed that patients receiving EGDT had higher costs and longer length of stay in the ICU (15).

IV immunoglobulin (IVIG) has also been studied as a treatment in sepsis. A 2013 meta-analysis of 43 randomized controlled trials (RCTs) including 25 RCTs of polyclonal IVIGs and 18 trials using monoclonal antibodies in adult and infant populations did not show any decreased mortality in the neonatal population. Although there was some evidence to suggest decreased mortality in adults when using immunoglobulin M enriched polyclonal IVIGs, the effect was not seen when accounting for low quality study design and bias (16).

Anti–tumor necrosis factor (TNF)-alpha antibodies have been presented as a possible sepsis treatment. TNF-alpha is a pro-inflammatory cytokine and has been implicated in the development of septic shock (17). There have been mixed results in trials. Early studies demonstrated failure to reduce mortality; however, in a recent meta-analysis, mortality was reduced by immunotherapy with anti-TNF-alpha monoclonal antibodies (18–21). Another anti-inflammatory therapy with interleukin (IL)–1 receptor antagonists has similarly failed to reduce mortality (22).

Currently, there are no effective anti-septic drug therapies due to complex inflammatory and metabolic interactions. Interventions during the early stages of sepsis with fluids, antibiotics, and EGDT have failed (23). It was suggested recently that pretreatment of neonatal mice with an aluminum salts-based adjuvants have been found to stimulate innate immunity through myeloid cell activation and improve survival in premature mice with sepsis (24). Further studies investigating the interface between key factors leading to organ dysfunction should be conducted to effectively address septic patient mortality rates.

## GENERAL PRINCIPLES OF IMMUNOMETABOLISM OF SEPSIS

Many conditions in humans are associated with cellular metabolic dysfunction of immune cells such as hyperlipidemia, diabetes, obesity, nonalcoholic fatty liver disease (NAFLD), and of course, sepsis (25). In hypercholesterolemia, cholesterol accumulation in immune cells that leads to atherosclerosis has been associated with activation of pro-inflammatory pathways such as Toll-like receptor (26). Although type 2 immunity that promotes an anti-inflammatory environment is predominant in the lean adipose tissue, increased energy storage in obesity has been related to adipocyte dysfunction and a pro-inflammatory state with cluster of differentiation 8+ (CD8+) T cells and M1-polarized macrophages with subsequent insulin resistance, liver inflammation leading to NAFLD and nonalcoholic steatohepatitis (27). The mammalian target of rapamycin (mTOR) pathway is a key modulator of metabolic function through the regulation glycolysis and oxidative phosphorylation (OXPHOS) and mTOR activation in CD4+ and CD8+ T cells also results in metabolic reprogramming and a switch to glycolysis for energy production (28).

In sepsis, there is an acute hyper-inflammatory phase characterized by elevated pro-inflammatory cytokines, hypercoagulability, and increased production of WBCs and platelets that are considered acute reactants. Obesity increases the interactions between the circulating and endothelial cells during sepsis (29). In a mouse model of obesity and sepsis, this inflammatory response is diminished by replacing adiponectin in both sirtuin 1-dependent and -independent mechanisms (29). We will discuss the role of sirtuins in sepsis immunometabolism below. At the same time, the expansion of myeloid-derived suppressor cells (MDSCs) negatively affects both the innate and adaptive immunity and promotes chronic immunosuppression. MDSCs share phenotype with monocytes and neutrophils and are divided into monocytic MDSCs and polymorphonuclear MDSCs (PMN-MDSCs) (30). Lectin-type oxidized LDL receptor 1, a receptor for oxidized LDL and expressed on endothelial cells, macrophages, and smooth muscle cells have been associated with PMN-MDSCs and their immunosuppressive properties (31). The expression of microRNAs miR-21 and miR-181b has been shown to induce the MDSC expansion in murine polymicrobial sepsis (32). The expression of these microRNA and the subsequent expansion of immunosuppressive MDSCs that occurs in late sepsis is mediated by the S100A9 protein which associates with Stat-3c/enhancer-binding protein-β in an IL-10-dependent pathway (33, 34). Although MDSCs are not usually found in healthy individuals, increased numbers of blood MDSCs in sepsis are associated with worse clinical outcomes, nosocomial infections, and mortality (35). MDSCs

have been well studied in cancer. Their maturation has been shown to be dependent on glycolysis and the glucose-derived carbon for carbon metabolism and adenosine triphosphate (ATP) generation while OXPHOS is only barely active in order to replenish NADPH. This metabolic activity is directly associated with tumor invasiveness with an indirect immunosuppressive state due to the apoptosis of immune cells because of the reduced availability of carbon (36).

The early inflammatory response is the first part of what was thought to be a biphasic septic response with an anti-inflammatory state characterized by increased production of anti-inflammatory cytokines, decreased expression of major histocompatibility complex by antigen-presenting cells, apoptosis of lymphocytes, and increased T-cell anergy to follow the hyperimmune phase. It is now described that both inflammation and immunosuppression occur at the same time and the term compensatory anti-inflammatory response syndrome (CARS) that initially defined the second phase of sepsis (mainly characterized by immunosuppression), has been replaced by the term mixed antagonist response syndrome that includes features of SIRS in patients with CARS. Concomitant activation of pro-inflammatory and anti-inflammatory pathways can lead to the persistent inflammatory, immunosuppressed, catabolic syndrome used for septic patients who stay in the ICU for more than 10 days (37–40).

The failure of current sepsis treatments may be attributed to the fact that changes in cell metabolic functions were not taken into account. Sepsis-related organ failure has been linked to hyperinflammation and energy deprivation (41, 42). The initial stage of septic shock is characterized by a hyper-inflammatory state due to the overexpression of pro-inflammatory cytokines such as IL-1, IL-6, and TNFα (43). This initial hyper-inflammatory phase has been associated with energy deprivation in animal models and can lead to direct organ damage and failure due to an increased metabolic demand (44). As a result, the body's energy production enters into an anaerobic state due to impaired OXPHOS. Consequently, this induces a metabolic shift and glycolysis becomes the primary metabolic pathway. During this phase, there is a decreased generation of ATP due to reduced oxidative metabolism (44). During sepsis, impaired OXPHOS may account for the compromised energy production in the heart, liver, kidneys, lungs, and brain for patients in septic shock and the development of end-organ dysfunction due to compromised fatty acid oxidation (FAO) and glucose catabolism (44, 45).

Sepsis-induced changes in FAO and OXPHOS have been related to the decreased expression of peroxisomal proliferator-activated receptor (PPAR)–γ and the diminished functionality of cellular mitochondria. The peroxisomal PPARs can be found in three isoforms: $\alpha$, $\beta/\delta$, and $\gamma$ (46). Their main role is to regulate the expression of genes involved in adipogenesis, lipid and glucose metabolism, inflammation, and the maintenance of metabolic homeostasis (46, 47). They can be activated by fatty acids and their metabolites act as lipid sensors that, when activated, can modulate metabolism (48–50).

PPARα is highly expressed in adipose tissue and skeletal muscle and mainly regulates genes activating lipid and lipoprotein metabolism (51–53). Early in sepsis, there is evidence for increased cardiac function in mice, however, with the absence of PPARα, by 24 hours, this increased function cannot be sustained (54). PPARα plays a central role in FAO. In lipopolysaccharide (LPS) sepsis models, the increased expression of PPARα might be responsible for the decreased expression of the necessary proteins needed for FAO (55, 56). The reduction in expression of those proteins may be mediated by c-Jun N-terminal kinase, as its inhibition can restore cardiac function in an LPS model of sepsis in mice, as well as increase PPARα levels (57). In a study that included pediatric patients, there was decreased PPARα in circulating leukocytes and worse outcomes in patients with the lowest PPARα expression (58). Similarly, PPARα knockout mice have decreased survival in sepsis, but this is not improved in chimeric mice with wild-type bone marrow, so it is hypothesized that it is the end organ expression of PPARα, and not the hematopoietic expression, that determines survival and cardiac function (59). Since PPARα expression is decreased during sepsis, the body depends on PPARγ to act as an alternative regulator of energy production.

PPARγ can be activated by a family of natural and synthetic ligands, such as glitazones, and can be an important tool to regulate energetic deficiencies in sepsis (41). PPARγ activation regulates cholesterol efflux in macrophages and thus reduces inflammation by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity (60). NF-κB is a prototypical transcription factor that promotes the expression of pro-inflammatory genes including those for cytokines, chemokines, and adhesion molecules. It plays a central role in coordinating inflammation and is a critical factor in the etiology of metabolic disorders (61). This presents an opportunity for new drug targets and the development of therapeutic approaches to treat complex disorders, such as sepsis. NF-κB is a stress-induced pathway (i.e., tissue damage, cytokine, and pathogen-associated molecular patterns release), which promotes the expression of target genes involved in the immune response (62). After activation of the NF-κB pathway and induction of cytokine expression, macrophages differentiate into the M1 or M2 subtype depending on the milieu of local cytokines that they are exposed to at the infection site. M1 cells are induced by interferon (INF)–γ and generally produce pro-inflammatory cytokines (61, 63). On the other hand, M2 cells encompass macrophages exposed to IL-4, IL-13, immune complexes, IL-10, and/or glucocorticoid or secosteroid hormones (61, 63). The pro-inflammatory cytokines and the NFκB signaling pathway are major players in the inflammatory process during sepsis. Studies have shown that this process can be counteracted when energy production is restored through PPARγ and PPARγ co-activator 1 alpha (PGC-1 alpha) agonism under septic conditions (41, 42, 64).

PPARγ can be activated by various natural ligands including fatty acids, nitrated fatty acids, and eicosanoid derivatives. Synthetic ligands include thiazolidinediones and some nonsteroidal anti-inflammatory medications, which could be used to regulate energetic deficiencies in sepsis (41). PPARγ agonists have improved survival in a rat and mouse models of sepsis (41, 65–67). Specifically, PPARγ activation ameliorates cardiac dysfunction in animal models of sepsis (41). This may be due, in part, to changes in metabolism during sepsis (68). It has also been reported that in a cecal ligation and puncture (CLP) model of sepsis in rats, PPARγ activation prevented cardiomyocyte apoptosis, necrosis,

and necroptosis (66). Although prior studies in mice showed no reduction in local inflammatory mediators (41), this rat CLP model demonstrated that pretreatment with a PPARγ agonist did decrease the local inflammatory response by preventing the degradation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha, which inhibits the NF-κB pathway, causing decreased IL-1β, TNF-α, and IL-6 in the myocardium (66). It should be noted that most of the animal experiments did not include treatment with fluids or antibiotics and that might have limited the generalization of results to humans.

Lymphocyte apoptosis during sepsis is well described. Although PPARγ may be anti-inflammatory in its role and help relieve the early hyper-inflammatory state during sepsis, there have also been studies that demonstrate that PPARγ activation induces apoptosis in lymphocytes, which could contribute to the immunosuppressive state found in later stages of sepsis (69–71). This idea, however, is controversial and some have argued that this cell death may be through PPARγ-independent mechanisms. It is worth noting that in the study by Soller et al (69), the apoptotic effect was reduced when a PPARγ antagonist was added.

PPARγ activation also regulates cholesterol efflux in macrophages and thus reduces inflammation by inhibiting NF-κB activity (60, 72). Recent research suggests that administration of a PPAR-γ agonist, rosiglitazone, can increase cardiac FAO, which leads to increased cardiac function and reduced mortality in mice (41). Fatty acids are normally shuttled into cardiomyocytes by CD36, very low-density lipoprotein receptor (VLDLR), and low-density lipoprotein receptor (LRP), but these are downregulated during sepsis. As a result, fatty acid content increases in circulation. Patients who die in septic shock appear to have increased intracardiomyocyte accumulation of lipids, indicating decreased FAO (73).

PPARα plays a central role in FAO but, as it remains decreased during sepsis, PPARγ becomes the alternative regulator. PPARγ agonism can restore the expression of VLDLR and LRP, resulting in improved energy production (41). Rosiglitazone is a PPARγ agonist and is an anti-diabetic drug from the thiazolidinedione class (74). It increases insulin resistance, but also appears to exhibit anti-inflammatory effects through NF-κB and increases gluconeogenesis (75). It demonstrates the ability to induce the PPARγ pathway through activation of the co-activator PGC-1 alpha (41). Those studies need to be replicated in humans in order to determine if PPARγ agonism will have similar effects in septic patients. It is also important to mention that sepsis is the host response to an infection is a key element in sepsis and that specific bacterial strains can have a direct effect on PPARγ. Two metabolites of intestinal bacteria, butyrate, and propionate, can lead to activation of PPARγ transcriptional activity and alter metabolic regulation, cell cycle, cell differentiation, and inflammatory response (76). It was recently identified that not only cytokines but also Krebs cycle intermediates can directly activate pro-inflammatory gene expression. Succinate and itaconate, both Krebs cycle metabolites, are involved in inflammatory and metabolic signaling with itaconate having mostly an anti-inflammatory role (77). Succinate has been characterized as the only direct link between the Krebs cycle and the mitochondrial respiratory chain. Pathophysiologic conditions such as hypoxia results in the backup of the complex II of the electron transport chain which leads to the buildup of succinate. This effect induces hypoxia-inducible factor-a (HIFa) via the generation of reactive oxygen species via the retrograde flow of electrons through complex I (77). Succinate is a major regulator of inflammation that converts into succinate oxidase resulting in decreased production of anti-inflammatory IL-10 (78). Succinate accumulation in LPS-activated macrophages also induces IL-1β, a central inflammatory mediator and primes the nucleotide-binding domain leucine-rich repeats family protein 3/caspase-1 inflammasome. The inflammasome is also activated by ATP and phagocytosed materials such as β-amyloid. These signals have been shown to involve metabolic reprogramming (32, 79). During the same process, itaconate is an important derivative of citrate that seems to be anti-microbial and inhibits the growth of *Mycobacterium tuberculosis* and *Legionella pneumophila* and has possible modulatory roles during Zika virus infection in murine neurons (32, 77, 79).

Similarly, acetate can induce INF-γ production in T cells through citrate production (80). It is evident that the mitochondrion is not only the energy hub but also the signaling hub that uses metabolites to affect the immune response in stress conditions (77). Furthermore, FAO can lead to inflammasome activation in inflammatory macrophages, but studies have also found FAO to be anti-inflammatory. In M2 macrophages, cells that participate in resolution of the inflammatory response, the Krebs cycle, and OXPHOS are intact and reprogramming of macrophages from pro-inflammatory M1 to anti-inflammatory M2 can be achieved by metabolites (81). M1 macrophages have impaired OXPHOS due to a Krebs cycle dysfunction and ATP production is predominantly based on glycolysis. Krebs cycle intermediates citrate and succinate in this case lead membrane biogenesis and HIF1α activation, respectively. In contrast with M1 macrophages, M2 macrophages have an intact Krebs cycle, are more plastic and OXPHOS is the main source of ATP generation (82).

In murine models, the acute phase of sepsis is characterized by metabolic reprogramming and a switch from OXPHOS to glycolysis, while in later stages, there are defects in both glycolysis and oxidative metabolism that can be partially corrected with recombinant INF-γ therapy (83). Not only is glycolysis pro-inflammatory, but it's also crucial for IL-4-induced macrophage activation via 2-Deoxy-D-glucose (83). The shift to glycolysis is required for the enhanced biosynthetic activity in activated dendritic cells and in murine models for LPS to induce IL-1β production (84). It is also interesting that cells also switch from glycolysis that is dominant during the acute inflammatory reaction to fatty acid β-oxidation in the postacute phase described as immunometabolic adaptation. This process is regulated by sirtuins 1, 3, and 6 (85). The sirtuins are a family of nicotinamide adenine dinucleotide (NAD+) sensing histone deacetylases that regulate inflammatory and metabolic responses to sepsis. Sirtuin 1 is also an important regulator of inflammation in sepsis with anti-inflammatory effects mainly through the deactivation of the NFkB pathway (86). Resveratrol, which induces sirtuin-1 expression has been shown to alleviate inflammation and improve survival in an obese septic mice (87). Sirtuin 6 has similar effects in NFkB (88).

The interaction between metabolism and innate immunity in sepsis is complicated and many parts remain unknown. An example

of this interaction is metabolites such as acetyl coenzyme A (acetyl-CoA), S-adenosylmethionine, a-ketoglutarate, NAD+, and polyamines than can directly affect the activity of chromatin-modifying enzymes and the production of certain pro-inflammatory cytokines. Interestingly, it has been described that cells during stress compete for the limited nutrients available and that can have marked effects on immune cell function (89). There are also other mechanisms by which metabolism and mitochondrial function can lead to cell death and organ failure in pathophysiologic conditions such as sepsis. Dysregulation of apoptosis, closely related to dysfunction of mitochondrial physiology as evidenced by impaired OXPHOS, oxygen radical generation and activation of mitochondrial permeability transition, is promoted by the release of mitochondrial death factors, such as cytochrome c, second mitochondria-derived activator of caspase/direct IAP binding protein with low pI, and serine protease Omi/high temperature requirement protein A2. Those factors are involved in caspase-dependent cell death mechanisms (90).

Another important process during sepsis needs further research in order to uncover mechanisms that can lead to therapeutic targets. Even after antimicrobial and supportive treatment has been initiated, affected organs keep releasing endogenous alarmin and activating danger-associated molecular pattern signaling that causes chronic inflammation and a shift toward myeloid cell production in bone marrow with a subsequent anemia and lymphopenia. This expansion of myeloid progenitors is mainly responsible for the persistence of immunosuppressive and catabolic states (91). The expansion of immature myeloid cells is induced by factors such as vascular endothelial growth factor, granulocyte-macrophage-colony-stimulating factor, macrophage colony-stimulating factor, and stem cell factor, (DAMPs), and chemokines (35). The chronic critical illness characterized by immunosuppression associated with continuous low-grade inflammation maintained by the release of damage-associated molecular patterns (DAMPs) and pro-inflammatory cytokines is also associated to iron-restricted anemia among critically ill septic patients even in the absence of systemic iron deficiency (92).

For all these years, we have neglected metabolic dysfunction as a key part of sepsis progression to multiple organ failure. There is still much research needed in this emerging field of immunometabolism in order to develop therapeutic approaches that account for the metabolic deficit as well as the effects of cell respiration to innate immunity. A summary of the most important studies mentioned above can be found in **Table 1**.

## THE NEED TO ADD METABOLIC DYSFUNCTION IN SEPSIS THERAPEUTICS

It is now evident that immune system signals can regulate metabolic pathways and metabolites and availability of nutrients can change cell function and gene expression. As stated above, one possible reason anti-inflammatory agents alone are inadequate to treat septic shock is that the "energetic starvation" of the heart and other organs that occurs at earlier stages of the condition has

**TABLE 1. Summary of Most Important Studies in Sepsis Immunometabolism**

| References | Summary |
|---|---|
| Pollizzi et al (28) | Mammalian target of rapamycin activation in CD4+ and CD8+ T cells leads to metabolic reprogramming and a switch to glycolysis for energy production |
| Hooftman et al (32) | Expression of miR-21 and miR-181b induce MDSC expansion in murine polymicrobial sepsis |
| Schrijver et al (35) | MDSCs are not found in increased numbers in septic patients and are associated with worse clinical outcomes, nosocomial infections, and mortality |
| Horiguchi et al (39) | The term compensatory anti-inflammatory response syndrome used for the second phase of sepsis (immunosuppression) has been replaced by persistent inflammatory, immunosuppressed, catabolic syndrome used for septic patients who stay in the ICU for over 10 d |
| Drosatos et al (57) | Inhibition of c-Jun N-terminal kinase can restore cardiac function in an LPS murine model of sepsis by increasing PPARα levels and subsequently fatty acid oxidation |
| Peng et al (66) | PPARγ activation in cecal ligation and puncture model of sepsis prevents cardiomyocyte apoptosis, necrosis, and necroptosis |
| Wang et al (75) | Rosiglitazone, a PPARy agonist, increases has anti-inflammatory effects through nuclear factor kappa-light-chain-enhancer of activated B cells and increases gluconeogenesis |
| Mills et al (78) | Succinate in LPS-activated macrophages induces interleukin-1β, primes the nucleotide-binding domain leucine-rich repeats family protein 3/caspase-1 inflammasome and is involved in metabolic reprogramming |
| Hooftman et al (32) | Itaconate is involved in metabolic reprogramming and has anti-microbial properties |
| Chang et al (89) | Certain metabolites such as acetyl coenzyme A, S-adenosylmethionine, a-ketoglutarate, nicotinamide adenine dinucleotide, and polyamines can directly affect the production of pro-inflammatory cytokines |
| Hawkins et al (91) | Even after treatment, affected organs in sepsis keep releasing endogenous alarmin and activating danger-associated molecular pattern signaling that lead to chronic inflammation and a shift toward myeloid cell production |

CD = cluster of differentiation, LPS = lipopolysaccharide, MDSC = myeloid-derived suppressor cell, miR = microRNA, PPAR = peroxisomal proliferator-activated receptor.

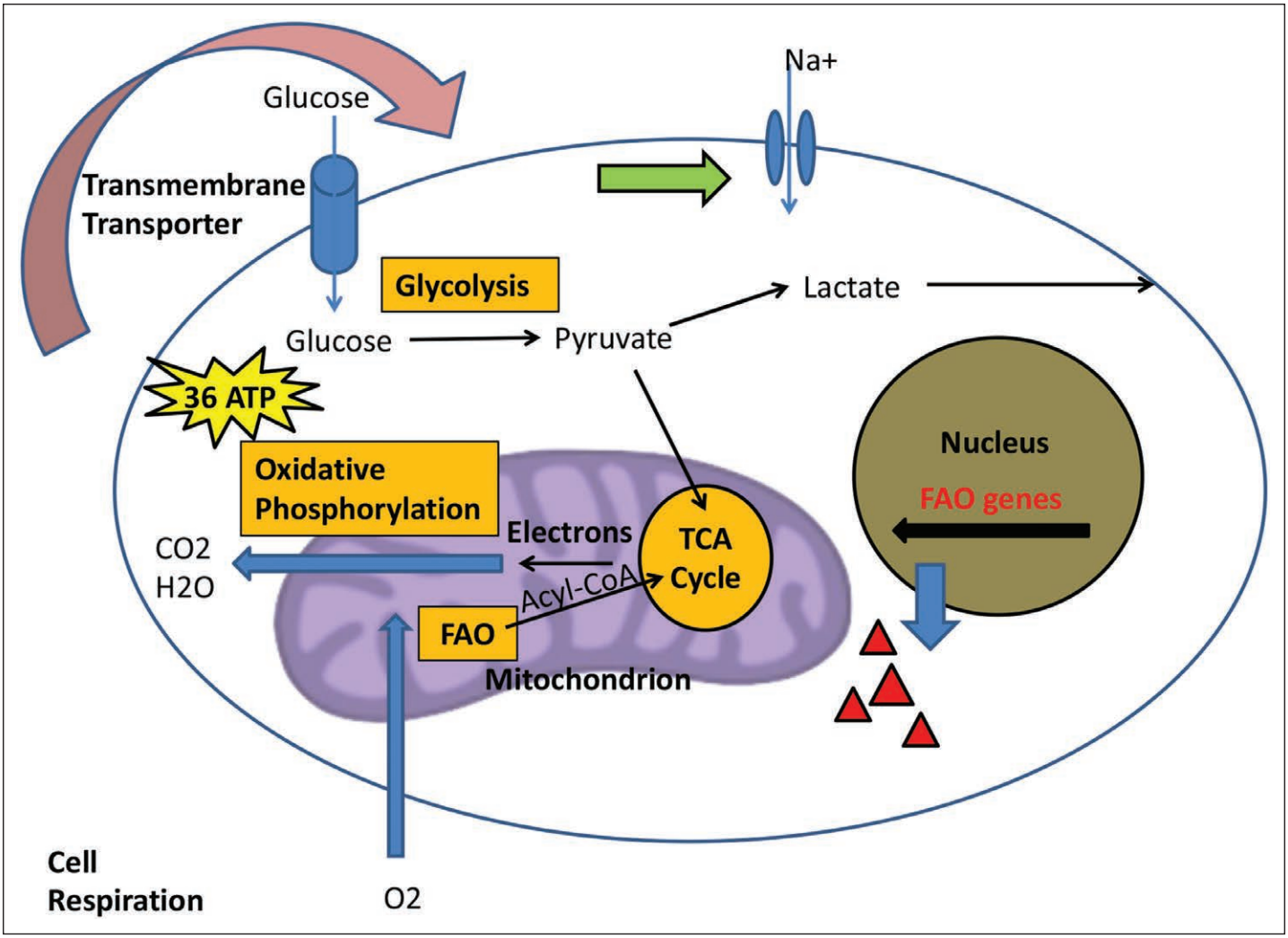


**Figure 1.** Schematic presentation of cell respiration during sepsis. There is a switch from energy efficient oxidative phosphorylation (36 adenosine triphosphate [ATP] molecules/molecule of glucose) to glycolysis that can generate only two ATP molecules per molecule of glucose. acyl-coA = acetyl coenzyme A, FAO = fatty acid oxidation, TCA = tricarboxylic acid.

not been taken into account. We propose that therapies should be guided toward treating this initial hyper-inflammatory state with a main focus on energy production. It is speculated that although inflammation improved with the use of some anti-inflammatory drugs, organ failure still progressed due to decreased ATP generation (37). In a study by Uji et al (93), when PPARγ activation was applied to mice that did not express adiponectin, an adipocyte-derived protein involved in FAO, survival did not improve. Reduced expression levels of fatty-acid-binding protein, acetyl coenzyme A synthetase, and carnitine palmitoyl transferase-1 were also linked to inadequate intracellular cardiac FAO leading to the conclusion that sepsis leads to an energetic deficit that might be linked to the immune response (94). Acetyl-CoA from FAO generally feeds into the Krebs cycle and electron transport chain in the mitochondria to produce ATP. It is important to mention that during sepsis, there is a switch from energy efficient FAO and OXPHOS to aerobic glycolysis. The difference in energy production is significant as OXPHOS can generate up to 36 ATP molecules per molecule of glucose, whereas glycolysis can only generate two ATP molecules per molecule of glucose (**Fig. 1**) (95).

The metabolic activity of PPAR-γ agonists is well characterized among animal models, but there are few existing human studies. Previous studies used either only human or animal cells while existing studies with human subjects lack the confirmation of those results. Rosiglitazone seemed to improve FAO oxidation in mice with a subsequent increase in survival, but its impact on the inflammatory process was not studied and may have significantly contributed to positive outcomes (41). If we can investigate the relationship between inflammation and metabolism, we may be able to make a breakthrough in treating septic patients and prevent an excessive inflammatory response.

## CONCLUSIONS

There is a unique relationship among the immunometabolic signaling pathways during the first phase of sepsis pathology based on previous work on animal models. If we can identify a similar relationship and mechanism of action, which is occurring early in the septic process in human models, we may be able to identify drug targets and improve the clinical outcome of patients with sepsis

and septic shock. Future studies should be guided toward using molecules such as PPARγ agonists in order to improve energy production at the cellular level which can concomitantly decrease the hyperimmune response with the goal of a favorable clinical prognosis. This would be the first step in assessing the possibility of using these and other molecules in the treatment of sepsis.

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