

Cellular metabolism of myeloid cells in sepsis

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ABSTRACT

In recent years, it has become appreciated that immune cells have different metabolic profiles depending on their activation status. During sepsis, circulating leukocytes go through a hyperinflammatory state, which can be accompanied or followed by defective antimicrobial defenses (also described as immune tolerance or paralysis). In this review, the modulation of different cellular metabolic pathways during sepsis in monocytes and macrophages will be discussed. Glycolysis is studied extensively in sepsis and is up-regulated in hyperinflammatory cells, whereas in immune tolerance, it is often down-regulated. Few data are available on other metabolic pathways in immune cells from patients with sepsis. The pentose phosphate pathway is up-regulated during acute hyperinflammatory responses, whereas fatty acid β -oxidation is increased later during sepsis and is associated with an anti-inflammatory (M2) phenotype of macrophages. Within the amino acid metabolism we will discuss the most studied metabolites. Collectively, these data argue that exploration of the immunometabolic pathways in sepsis is an important area of research, and the targeting of metabolic pathways may represent a promising novel strategy as a therapy of sepsis. *J. Leukoc. Biol.* 101: 151–164; 2017.

Introduction

The need to be able to adapt quickly to new circumstances (e.g., infection or trauma) conveys that leukocytes are extremely dynamic. This phenotype skewing of leukocytes is highly dependent on environmental signals during the differentiation process. Recently, it has become apparent that the phenotype and the activation state of leukocytes correlate with their specific metabolic profile [1, 2]. A summary of the changes in metabolic pathways in various states of immune cells is provided (see Fig. 1).

During sepsis, monocytes and macrophages will encounter a state of hyperinflammation, characterized by excessive release of inflammatory mediators. Often, this progresses toward a

dysfunctional state, in which cells are unable to respond properly to stimulation—immune tolerance or paralysis [3]—that is associated with an increased susceptibility to opportunistic infections. These states can both overlap and occur subsequently [3, 4]. Moreover, it has been suggested recently that immune cells can display different metabolic profiles depending on their immunologic states during sepsis [5]. Therapeutic modulation of leukocyte metabolism could potentially improve the outcome of sepsis by altering the inflammatory responses leading to septic shock or reverse immunotolerance.

This review focuses on the immunometabolic changes in monocytes and macrophages during sepsis. We will discuss the present literature on regulation of glycolysis, PPP, TCA cycle and OxPhos, amino acid, fatty acid, and cholesterol metabolism during sepsis and immunotolerance. Furthermore, the interactions between cellular metabolism and epigenetic reprogramming of monocytes and macrophages will be discussed. Finally, the therapeutic potential of influencing immunometabolism in sepsis will be highlighted.

CELLULAR METABOLISM IN IMMUNE CELLS

The research on the metabolic pathways in immune cells is a rapidly evolving field that started with the description of metabolic states of different types of lymphocytes. Activated T lymphocytes have high rates of both glycolysis and OxPhos and metabolize glucose to lactate [6, 7], whereas memory T-lymphocytes are more dependent on lipid synthesis via mitochondrial citrate production. These lipids can be used to produce triacylglycerides, which are being degraded by β -oxidation to fuel OxPhos via acetyl-CoA production [8]. In contrast, regulatory T cells fuel β -oxidation and OxPhos through exogenously derived fatty acids [9]. This shows that the phenotype of lymphocytes highly correlates with the source of energy that they use [1, 10].

Over the last years, knowledge of macrophage metabolism has also vastly expanded. Proinflammatory (M1) macrophages increase their glucose metabolism and lactate production via glycolysis, whereas the more anti-inflammatory (M2) macrophages rely on OxPhos [11, 12] and β -oxidation by fatty acid uptake [13].

Abbreviations: AMPK = AMP-activated protein kinase, BMDM = bone marrow-derived macrophage, CARL = carbohydrate kinase-like protein, CLP = cecal ligation and puncture, CLR = C-type lectin receptor, CPT = carnitine palmitoyltransferase, CR = complement receptor, DCA = dichloroacetate, ETC = electron transport chain, G6P = glucose-6-phosphate, G6PD = glucose-6-phosphate dehydrogenase, GLUT = glucose transporter,

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This review will focus on the metabolic changes in macrophages and monocytes during sepsis.

SHIFTS IN GLYCOLYSIS

Glucose dissimilation via glycolysis is one of the basic metabolic processes in human cells to obtain energy in the form of ATP. Glucose is imported into the cell by GLUT1, whose expression is highly dependent on the activity of the transcription factor Hif1 α [14, 15]. Following uptake, glucose is converted into pyruvate by a series of enzymatic reactions, among others, the rate limiting steps of the enzymes HK and PFK. Pyruvate can either be converted into lactate by a process called lactic fermentation via anaerobic glycolysis, which yields a total of 2 ATP, or alternatively, can be converted into acetyl-CoA and enter the TCA cycle, which will eventually yield 36 ATP by OxPhos. As fermentation is, despite its lower ATP yield, faster in generating ATP and can become highly up-regulated following stimulation, this rapid ATP generation might be more favorable in situations that demand energy in a short timeframe, such as acute inflammation. In contrast, the TCA cycle and OxPhos are more efficient in terms of ATP yield, but the reaction is significantly slower. A classic and well-known metabolic phenotype is the Warburg effect, which is a shift from OxPhos to glycolysis and enhanced lactate production and therefore, a faster ATP production, even in the presence of oxygen [16–19]. This phenotype was first observed in cancer cells but later, also in leukocytes upon activation.

During sepsis, monocytes have distinct phenotypical differences between the hyperinflammatory and the immunotolerant state [3]. Although the transition from hyperinflammation to immunotolerance is not a clear biphasic reaction but may overlap [3, 4], a differential capacity to produce cytokines is observed between these phenotypes [3]. Along with these differences in cytokine production, a clear difference in cellular metabolism can be observed [5]. Upon activation, monocytes become hyperinflammatory, and glycolysis is up-regulated, resulting in increased lactate production through a Hif1 α -dependent pathway that up-regulates expression of GLUT1, PFK, and PDK [20–26]. Likewise, LPS-stimulated BMDM shows an increase in GLUT1, HK3, third isoform of human 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase, phosphoglycerate mutase 2, and enolase 2 expression [27, 28], and this has been shown to contribute to an increased IL-1 β and IL-6 production [27]. During the acute hyperinflammatory phase of sepsis, the transcriptional profile of leukocytes displays a significant increase in genes

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GPC = glycerophosphocholine, HDAC = histone deacetylase, Hif1 α = hypoxia-inducible factor 1 α , HK = hexokinase, HLA-DR = HLA-antigen D related, HMGB1 = high-mobility group box 1, ICU = Intensive Care Unit, LPC = lysophosphatidylcholine, M1 = classical macrophage, M2 = alternative macrophage, MCAD = medium-chain acetyl-CoA dehydrogenase, mTOR = mammalian target of rapamycin, OxPhos = oxidative phosphorylation, PDK = pyruvate dehydrogenase kinase, PFK = phosphofructokinase, PGC = peroxisome proliferator-activated receptor- γ coactivator, PHD = prolyl hydroxylase, PKM2 = pyruvate kinase alternative macrophage, PPAR = peroxisome proliferator-activated receptor, PPP = pentose phosphate pathway, PRR = pattern recognition receptor, ROS = reactive oxygen species, SAM = S-adenosyl methionine, SIRT = sirtuin, TCA = tricarboxylic acid (or Krebs), TET = ten-eleven translocation

required for glycolysis [20, 29], whereas later during the immunotolerant state, genes regulating glycolysis are down-regulated [5, 20] (Fig. 1).

Interestingly, hyperlactatemia is a symptom of sepsis, which used to be interpreted as a result of tissue hypoperfusion and therefore, tissue hypoxia [30]. However, aerobic glycolysis and lactate production are also increased in monocytes and lymphocytes upon stimulation [30–34]. It has thus been suggested that at least some of the increased serum lactate during sepsis could originate from activated immune cells.

PDK regulates the conversion of pyruvate to acetyl-CoA, which enters the TCA cycle. DCA, an indirect activator of PDK, decreased lactate levels and increased glucose levels in muscles of rats during sepsis but did not alter plasma lactate levels [23]. In septic patients, DCA was able to reduce lactate production and glucose consumption in whole blood [35]. In line with this, a recent case report also showed that a child treated with propranolol (a β -blocker that is also an inhibitor of glycolysis) was unable to develop hyperlactatemia during severe septic shock [36]. Comparable septic patients with long-term β -blocker therapy showed lower lactate concentration upon presentation, most likely as a result of inhibition of glycolysis. Interestingly, these lower lactate levels tended to correlate with lower mortality [37], but whether this is a result of reduced inflammation or a direct effect of lactate remains to be determined.

As one of the last enzymes in the glycolysis pathway, PKM2 has been shown to play a crucial role in mediating aerobic glycolysis in RAW 264.7 macrophages and BMDMs. PKM2 stabilizes Hif1 α to activate essential enzymes in the glycolysis pathway leading to lactate production [38]. Furthermore, it regulates release of HMGB1, an important danger-associated molecular pattern in sepsis. Promisingly, PKM2 inhibition reduced serum lactate and HMGB1 levels and protected mice from lethal endotoxemia [19]. Ethyl pyruvate has similar effects, as it inhibits the NF- κ B activation and reduces proinflammatory cytokine production and HMGB1 secretion [39], which might, at least partially, be a result of its inhibitory effect on PKM2 [40].

Macrophages of amyloid beta A4 precursor protein-binding family A member 3 (APBA3; an inhibitor of factor inhibiting Hif-1) knockout mice were demonstrated to have reduced ATP levels and decreased glycolytic activity as a result of decreased expression of Hif1 α -activated genes [41]. During LPS-induced septic shock, these mice showed decreased glycolysis, cytokine production, and mortality [42].

Caspase-1 in THP-1 cells is required for cleaving pro-IL-1 β into its active form; however, it can also cleave several enzymes in the glycolysis pathway [43]. Interestingly, caspase-1-deficient mice are protected from septic shock-induced mortality [44, 45], which has been suggested to be independent from the caspase-1 effect on pro-IL-1 β or pro-IL-18, as *IL1B/IL18* double-knockout mice were not protected [46].

Data on glucose metabolism in cells with an immunotolerant phenotype during sepsis are unfortunately scarce. We have recently shown that glycolysis and mTOR pathway signaling are down-regulated in patients with *Escherichia coli* and *Candida spp* sepsis [5]. We have proposed recombinant IFN- γ as a potential immune modulator during the immunotolerant state of sepsis. By treating fungal sepsis patients and endotoxemia-induced

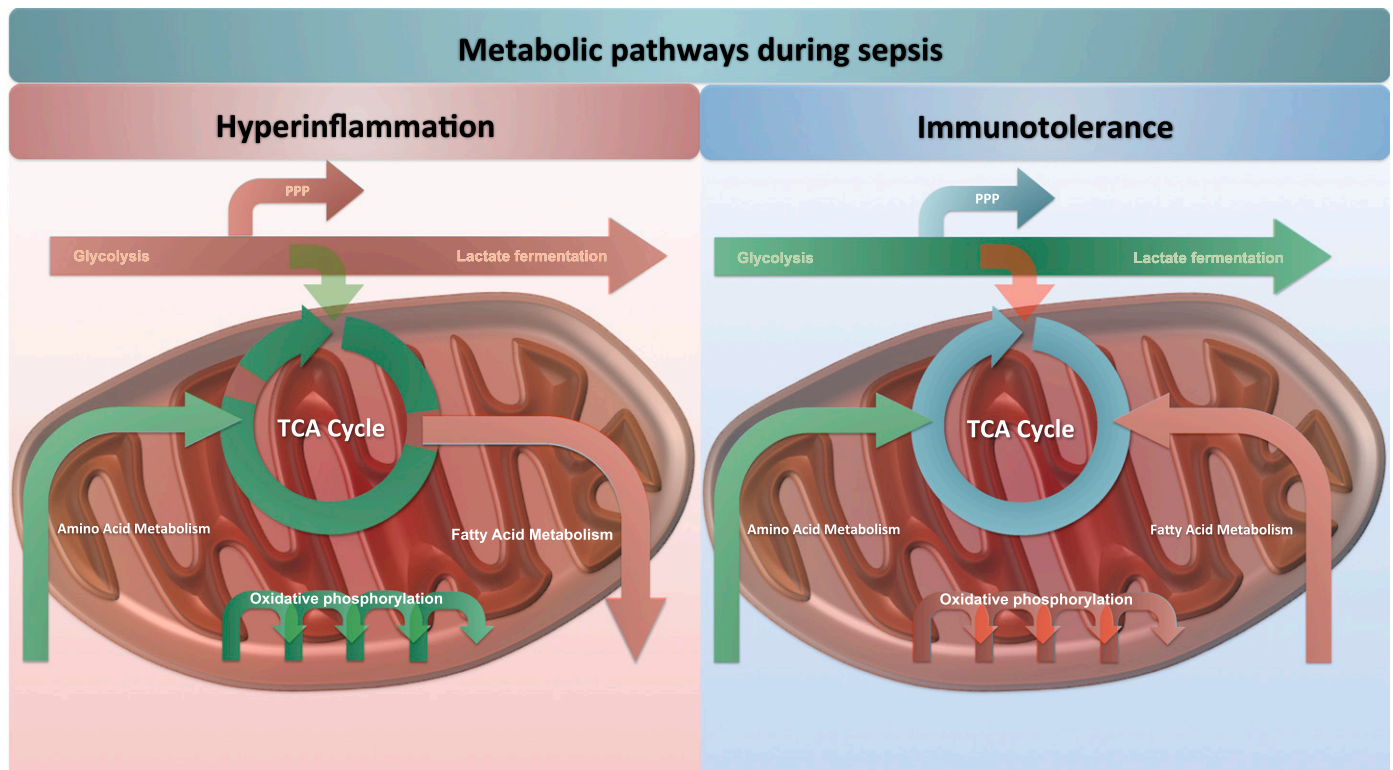


Figure 1. Metabolic changes in sepsis. Overview of global metabolic changes in monocytes during hyperinflammatory and immunotolerant stages of sepsis, although these stages can occur concurrently. Red, Up-regulated; green, down-regulated; blue, unknown or unchanged. During immunotolerance in vivo, broad metabolic defects in the monocytes have also been observed, where all metabolic pathways are down-regulated [5].

immunotolerant volunteers with IFN- γ , we were able to restore partially cytokine production [47, 48] and lactate production via glycolysis, by induction of the mTOR pathway [5]. In contrast, no effect of IFN- γ on OxPhos was observed. Interestingly, fructose-1, 6-diphosphate, one of the intermediates in the glycolysis pathway, has been proposed earlier as a treatment in endotoxin-induced septic shock [49], as it positively regulates glycolysis by stimulating PFK (one of the severely affected genes in sepsis) [5] and decreasing lipid metabolism [50, 51].

Given these promising results of modulating immunometabolism during sepsis-induced immunotolerance, we believe that modulation of immunometabolism may prove a promising approach for the treatment of sepsis.

PPP

The PPP is a metabolic pathway also emerging from glycolysis. HK (the first enzyme in glycolysis) converts glucose into G6P, which can be metabolized further into fructose-6-phosphate. Alternatively, G6PD can dehydrogenate G6P, which initiates the PPP. The PPP is divided into 2 branches: the oxidative and nonoxidative branches, which are used to generate NADPH for fatty acid synthesis and ribose-5-phosphate for the production of nucleotides. The non-oxidative branch can also shuttle metabolites back to glycolysis.

In a CLP model in rats, an increased peritoneal macrophage glucose consumption and lactate production were observed, combined with a significant increase of the pentose shunt [33].

G6PD was found increased in liver homogenates of endotoxin-treated rats and LPS-treated murine macrophages [28, 52], although this is in contrast to others, who showed a minor decrease in PPP fluxes after LPS stimulation of the murine RAW 264.7 macrophage cell line [53].

The sedoheptulose kinase CARKL, one of the kinases in the PPP, is down-regulated upon LPS administration in mice and humans [54]. CARKL overexpression was correlated with a more anti-inflammatory (M2) phenotype of macrophages, and down-regulation upon LPS stimulation was associated with a pro-inflammatory phenotype (M1). Moreover, CARKL appeared to colocalize with G6PD and to catalyze a reaction in the PPP, which functions as a bridge between glycolysis and PPP.

Altogether, an increase in PPP is observed during stimulation with LPS, concomitantly with an increase in glycolysis. No data are available on PPP during the immunotolerant state of monocytes and macrophages in sepsis (Fig. 1).

TCA CYCLE/OxPhos

The TCA cycle is considered a connecting part of different metabolic pathways. Glycolysis fuels the TCA via pyruvate and acetyl-CoA, glutamine can be converted via glutamate into α -ketoglutarate, which is an intermediate of the TCA cycle, and β -oxidation of fatty acids will also result in acetyl-CoA production. In the TCA cycle, metabolites are reduced by structural modifications and CO₂ production (and therefore, loss of carbon atoms), which results in production of GTP, NADH, and reduced flavin adenine

dinucleotide 2. The latter two will be used in the ETC to generate ATP molecules, a process that is called OxPhos that uses O_2 .

As previously indicated, monocytes and macrophages activated by LPS obtain a phenotype similar to a typical Warburg effect, with an increase in glycolysis and decrease of OxPhos [19, 20, 27, 55, 56]. Although during the Warburg effect, the TCA cycle is down-regulated, LPS-stimulated BMDMs show an increase of the TCA cycle metabolites succinate, malate, and fumarate [27] (Fig. 1). Succinate is of specific interest, as when it is transported to the cytosol, it can inhibit PHD, which results in stabilization and thus, activation of Hif1 α , contributing to the induction of IL-1 β production. This stabilization of Hif1 α by succinate is also indirectly ROS dependent, by decreasing Fe^{2+} , a cofactor necessary for PHD activity [57, 58]. In addition, increased succinate levels result in increased lysine succinylation, which is especially interesting, as many proteins in amino acid metabolism, TCA cycle, fatty acid metabolism, as well as PDK are some of its main targets [59]. Succinate was shown to be partially derived from glutamine by the GABA shunt (the metabolic pathway from glutamine toward succinate production). Inhibition of this metabolic pathway led to lower succinate levels, less Hif1 α stabilization, and lower IL-1 β production, both in BMDMs and murine sepsis. Moreover, inhibition of the GABA shunt resulted in reduced mortality in murine sepsis, just as observed in Hif1 α -deficient mice [2, 27, 60]. In contrast, the TCA cycle metabolite α -ketoglutarate can inhibit Hif1 α and IL-1 β induction [27, 61, 62].

The TCA cycle metabolite citrate accumulates in LPS-stimulated macrophages and has been shown to be essential for the production of NO, ROS, and PGs [27, 63, 64]. The TCA cycle enzymes isocitrate dehydrogenase 2 and citrate synthase are up-regulated after LPS stimulation of THP-1 cells in a SIRT3-dependent manner [20]. Furthermore, the mitochondrial citrate transporter citrate carrier, which transports citrate out of the mitochondrion into the cytosol, is up-regulated following LPS stimulation, and inhibition of this transporter resulted in less NO, ROS, and PG production [63]. Once in the cytosol, citrate can be metabolized into acetyl-CoA and oxaloacetate, which can be used for synthesis of NO, ROS, and arachidonic acid [65]. An increase of citrate and oxaloacetate was also found in an experimental rat model with *Klebsiella pneumoniae* bacteremia [22].

OxPhos is considered to be reduced in LPS-stimulated macrophages, displaying the classic Warburg effect [19, 20, 27, 55, 56]. In sepsis patients, mitochondrial dysfunction is observed, with decreased leukocyte oxygen consumption [5, 66–71]. However, others found an increased respiratory capacity in monocytes and PBMCs of septic patients [20, 72–74]. Moreover, data in the literature on total body oxygen consumption are variable, with some studies showing increased consumption in severe sepsis (but lower than in uncomplicated sepsis) [75], whereas others have reported decreased oxygen consumption [76]. In a study with almost 200 sepsis patients, complex-V activity (of the ETC) of platelets was decreased compared with healthy controls [77–79]. Reduced complex-V activity was also observed in a polymicrobial murine sepsis model. Interestingly, when these mice were treated with metformin (an AMPK activator), this increased complex-V activity and increased amounts of complex III and IV, resulting in decreased development of endotoxin-tolerant macrophages [80]. These data suggest that both the

timing of assessment and the type of cell and tissue are crucial for determining the extent of OxPhos activation in sepsis.

AMINO ACID METABOLISM

Amino acids are required for protein synthesis, but apart from that, amino acids can also be used as an energy source and are necessary for NO production [81]. Research has mainly been focused on supplementation therapy in septic patients and how this influenced outcome.

In a study with 35 sepsis patients, 42 aa were measured in serum at several time points after admission to the ICU. At admission, the amino acids arginine, aspartic acid, ethanolamine, glutamine, glutamic acid, homocitrulline, phenylalanine, and taurine were increased compared with controls. A decrease was seen in anserine, asparagine, carnosine, citrulline, cystathionine, histidine, isoleucine, leucine, lysine, ornithine, phosphoethanolamine, proline, sarcosine, threonine, tryptophan, tyrosine, and valine [82]. Furthermore, in a rat sepsis model, 2 h after cecal ligation, proline and valine were decreased significantly [83]. During progression of sepsis of the patients, amino acids were measured at 6 time points (up to 14 d) [82]. Severe sepsis resulted in increased levels of 3-methyl-L-histidine, α -amino adipic acid, α -amino-*n*-butyric acid, argininosuccinic acid, β -amino-isobutyric acid, carnosine, cystathionine, glutamine, phenylalanine, and proline at least 1 of the time points, whereas levels of arginine, asparagine, aspartic acid, cystine, glutamic acid, leucine, serine, taurine, and tryptophan showed lower concentrations, which were partially comparable with a similar study [84]. Interestingly, serum taurine levels in the severe sepsis group were significantly lower than those in the control group at all measured time points, and the cystine concentration was lower at 4 time points. The underlying mechanisms for the changes in serum amino acid levels during sepsis remain to be fully determined but are suggested to be a result of an imbalance between catabolism and anabolism during the inflammatory state of sepsis [82]. Interestingly, these changes can serve as a discriminator for survival—lower taurine and cystine levels correlated with mortality [82]. The changes in serum amino acid levels that are evidently reported [82, 84] can have a drastic impact on the metabolic pathway of immune cells, thereby altering the inflammatory state of cells. The amino acids that can alter inflammation during sepsis are detailed below.

In an in vitro study, taurine itself did not influence the production of TNF- α or NO by RAW264.7 macrophages, but taurinechloramine, a metabolite of taurine, attenuated TNF- α and NO production [85]. Moreover, in murine peritoneal macrophages and the macrophage cell line J774.2 production of TNF- α , NO, IL-6, and PGE₂ were attenuated by taurinechloramine [86, 87].

Arginine is of specific interest, because of up-regulation of arginase in M2 macrophages during sepsis [88, 89]. In several studies, arginine was demonstrated to be decreased during sepsis, as reviewed by Su et al. [82] and Davis and Anstey [90]. Several organs and tissues can contribute to reduced arginine levels, and additionally, monocytes and macrophages might play a role. Upon macrophage stimulation, arginine is imported by NOS2 to synthesize NO, which is released by M1 macrophages [91, 92].

Upon stimulation of macrophages, up-regulation of NOS2 is accompanied by induction of the arginine transporter cationic amino acid transporter 2 [93, 94]. In M2 macrophages, arginase is up-regulated, which provides another competing arginine metabolism pathway, resulting in a relative arginine deficiency for NO production [95]. BMDMs, from arginase-deficient mice, show increased cytokine and NO responses to LPS stimulation, whereas *Nos2*-deficient mice showed an opposite phenotype [96]. The exposure of murine macrophages to arginine decreases proinflammatory cytokine and NO production upon LPS stimulation [97]. Furthermore, citrulline availability is reduced in sepsis [98, 99], which might impair de novo synthesis of arginine [100]. Importantly, decreased citrulline levels during sepsis were associated with a higher mortality [84, 101, 102]. A detailed description of citrulline and arginine metabolism in sepsis is given in the review by Wijnands et al. [103].

Septic shock is also associated with an increase of nitrite and nitrate, which are reaction products of NO [104], and endotoxin and certain cytokines have in vitro been shown to induce iNOS and therefore, NO production in macrophages [105]. iNOS knockout mice showed greatly reduced symptoms and mortality compared with wild-type mice in LPS-induced sepsis [106]. However, there are also several studies that show little or a negative effect of NOS inhibition (listed in ref. [104]). It might be possible that the ambiguous effect of NOS inhibition is a result of at which time point it is impacted. On the one hand, it might be beneficial by reducing hyperinflammation, but on the other hand, it also might be detrimental when inflammatory responses are required for clearance of invading pathogens.

With the consideration of the decreased availability of several amino acids, supplementation regimens have been studied for their therapeutic potential. Enteral feeding, supplemented with, among others, arginine and ω -3-fatty acids, was shown to improve survival of septic ICU patients [107]. Arginine supplementation had no effect on immune function and development of nosocomial infections in ICU patients with a so-called arginine deficiency syndrome determined by low nasal NO concentrations [108]. Furthermore, the amino acid glutamine has also been shown to be essential for NO production by macrophages, together with arginine and citrulline [109].

The effects of glutamine on immune function and during sepsis have been studied extensively [110–112]. Intravenous administration of glutamine in rats, 1 h after cecal ligation, reduced organ injury, which was accompanied by a reduced neutrophil infiltration and IL-6 production in lungs, whereas a greater number of both M1 and M2 macrophages were observed [113]. In a comparable sepsis model, in which rats were parentally supplemented with glutamine from the moment of cecal ligation, lower plasma levels of proinflammatory cytokines, increased neutrophil phagocytosis, and increased survival were observed [114, 115]. However, a third comparable study demonstrated no effect on overall mortality, but phagocytic activity of peritoneal macrophages was decreased [116]. In neonatal rats, glutamine supplementation had beneficial effects on survival of sepsis [117]. When peritoneal macrophages of malnourished mice were supplemented with supraphysiological concentrations of glutamine, this significantly decreased LPS-induced TNF- α production, which was attributed to decreased

NF- κ B activation [115, 118, 119]. Interestingly, however, monocyte-derived macrophages showed lower HLA-DR, ICAM-1, Fc γ R, and CR3 and CR4 expression after lowering glutamine concentration in the culture medium. In addition, intracellular ATP concentrations were reduced [120]. Others have reported an induction of cytokine production after glutamine supplementation in LPS-induced acute lung injury [121] or different effects in vitro (increased TNF- α production) versus in vivo (decrease) of macrophages [122]. Inhibition of the GABA shunt reduced LPS-induced IL-1 β production in murine BMDMs [27]. The immunomodulatory role of glutamine might, therefore, be very well dependent on the exact moment of supplementation and the state of monocytes and macrophages at that specific moment.

Glutamine supplementation in patients was generally associated with positive-outcome measures. When critically ill patients at the ICU were supplemented with glutamine, they had an improved 6 mo outcome, potentially as a result of less (severe) infections [123, 124]. In a randomized clinical trial in multitrauma patients, glutamine-enriched enteral nutrition reduced infectious morbidity [125]. These positive effects might be a result of a high consumption of glutamine during the acute phase of immune activation and therefore, an intracellular shortage afterwards, which impairs the key functions of immune cells [110, 111, 126, 127].

Tryptophan is an essential amino acid that cannot be de novo synthesized and is metabolized by the enzyme IDO [128]. Several models in IDO-deficient mice show significantly reduced serum levels of IL-6 and IL-12, which improved sepsis survival [129–131]. IL-6 production of murine macrophages is IDO dependent, and tryptophan supplementation in vitro increases IL-6 (and also partially TNF- α and IL-12) production of macrophages [132]. Therefore, consumption and thus, intracellular depletion of tryptophan could lead to immunotolerance, just as seen in the tumor microenvironment [132, 133], and might serve as a potential therapeutic target. In a trial with 36 sepsis patients, an increase in IDO activity in whole blood was observed, which could be attenuated by GM-CSF treatment. Interestingly, IDO activity positively correlated with procalcitonin and negatively with monocyte HLA-DR levels (a marker for immunotolerance) [92]. Unfortunately, this study was too small and too short to observe clinical outcome measures.

A potential role in immunomodulation in sepsis was described for glycine. In a postoperative inflammatory ileus mouse model, glycine was shown to decrease IL-6, MCP-1, and MIP-1 α at tissue level [134]. Rats fed a glycine-rich diet showed lower and delayed TNF- α serum levels after LPS-induced sepsis and improved survival [135, 136], which might be a result of a glycine-gated chloride channel in Kupffer cells, which prevents the increase of intracellular Ca²⁺ and therefore, reduced cytokine production [137]. A similar mechanism has been observed in alveolar macrophages and neutrophils [138–140]. Glycine was observed to decrease significantly CD11b/CD18 expression and *E. coli* phagocytosis by monocytes and similarly decreased LPS-induced TNF- α production and increased IL-10 production [141].

The data described in this section illustrate the complexity of amino acid metabolism during sepsis, and they demonstrate that several amino acids have differential effects, depending on the time point during sepsis when the analysis is performed. However, a number of arguments support the claim that critically ill patients

can benefit from supplementation of amino acids, such as arginine, glutamine, cystine, and taurine, as randomized clinical trials demonstrated beneficial effects, such as reduced length of stay and secondary infections in sepsis patients [107, 142–148].

FATTY ACID METABOLISM

Fatty acids can either be used as an energy source (β -oxidation), or they can be synthesized from acetyl-CoA. During sepsis, β -oxidation in macrophages is an important metabolic process and therefore, has been well described. β -Oxidation mainly starts with triglycerides, either from meals or from adipose tissue, that are freed from glycerol by lipolysis. This process yields 3 free fatty acids that can enter the monocyte or macrophages by fatty acid transporters (e.g., CD36). Once inside the cell, the long-chain fatty acids are converted into fatty acyl-adenylates, which are fused with the CoA molecule to yield acyl-CoA, which is fused with carnitine by CPT-I, and this acyl-carnitine molecule is shuttled into the mitochondrion in exchange for a carnitine molecule by CPT-II. Once inside the mitochondrion, acyl-CoA is freed from carnitine, and β -oxidation can be initiated. Acetate molecules (consisting of 2 carbon atoms) are cut from the fatty acid chain and combined with CoA to form acetyl-CoA, which enters the TCA cycle, while fusing with oxaloacetate to form citrate. Each 2 carbon atoms cut from a fatty acid chain will result in production of 5 ATP molecules [81, 149].

In LPS-stimulated BMDMs, increased citrate and fatty acids levels were observed, suggesting a diversion from the TCA cycle toward fatty acid synthesis during the acute-phase response [27, 150]. In the THP-1 cells, LPS stimulation leads to an acute up-regulation of glycolysis, which transited into an increased fatty acid β -oxidation. This shift was characterized by PGC-1 α and β -mediated up-regulation of CD36 and CPT-I, which on its turn, was induced by SIRT1. A similar pattern was observed in human leukocytes from sepsis patients and in murine sepsis splenocytes [20, 24, 151, 152].

This observation relates to induction of M2 or anti-inflammatory macrophages by stimulation with IL-4, which results in activation of STAT6 and PGC-1 β , inhibiting proinflammatory cytokine production and glycolysis, whereas fatty acid uptake and oxidation and expression of MCAD, CPT-1, and CD36 are strongly up-regulated [153–157].

In a metabolomics and proteomics study on plasma in >1000 sepsis patients, fatty acid metabolism was defined as one of the most promising metabolic predictors for survival in sepsis. Six carnitine esters were found to be decreased in sepsis survivors relative to controls and 16 carnitine esters and 4 fatty acids to be elevated in nonsurvivors. Nine fatty acid transport proteins were decreased in nonsurvivors, showing that fatty acid β -oxidation is severely impaired in sepsis nonsurvivors [158], a pattern that had also been observed upon LPS stimulation of murine kidneys [159]. In several animal models, CPT-1 and MCAD expression was decreased in liver, kidney, and heart, which was dependent on decreased expression of PPARs [159–162]. In a rat sepsis model, several fatty acids were shown to be significantly up-regulated in serum, 2 h after cecal ligation [83]. Furthermore, PPAR α expression was shown to correlate with survival during murine septic shock [163]. This is of specific interest, as PPARs are known to regulate fatty acid β -oxidation and the expression

of MCAD [164, 165]. In human sepsis, transcriptome analysis has shown a profoundly decreased expression of genes regulating β -oxidation, which was accompanied by a decreased CPT-I and CD36 expression in human tolerant monocytes. This was restored upon recovery of the patients [5]. Therefore, it could be concluded that β -oxidation is down-regulated during severe sepsis but enhanced in M2-type macrophages (Fig. 1).

Interestingly, in a zebra fish LPS-stimulation model, during the acute phase (4 h after stimulation), transcription of several enzymes in fatty acid metabolism was significantly up-regulated, whereas most of these genes were down-regulated during the immunotolerant state, which especially accounted for genes involved in cholesterol synthesis [25]. Pretreatment with statins in murine *Staphylococcus aureus* and *K. pneumoniae* sepsis increased survival by dampening macrophage responses to the bacterium and by down-regulating the MHC class II molecule and CD80 and CD86 expression on T cells [166, 167].

When metabolites were assessed in plasma of >1000 patients, a vast decrease in glycerophosphoethanolamide and GPC esters was observed in septic patients, which was consistent with the observation that these esters were predictive for sepsis mortality [158, 168]. Supplementation with exogenous stearyl-GPC has been shown to improve outcomes in septic mice [169]. In humans, only free fatty acid supplementation has been studied in acute lung injury, which did not have any effect [170].

As a result of the changes in fatty acid metabolism during sepsis, therapy with various fatty acids has been investigated as a potential treatment. In a murine cecal ligation model of sepsis or upon intraperitoneal injection with *E. coli*, supplementation with LPC, an endogenous lysophospholipid, was able to decrease mortality. Intraperitoneal *E. coli* clearance was increased, which was mainly a result of decreased neutrophils deactivation [169]. Moreover, LPC significantly decreased HMGB1 release from monocytes and macrophages in murine endotoxemia and sepsis [171] and reduced circulating IL-1 β levels, subsequently diminishing organ injury and dysfunction [172]. Supplementation with ω -3-fatty acid supplements has been shown to be beneficial on several outcome measures in sepsis patients—among others, less secondary infections and shorter ICU stay [107, 173, 174]. In vitro, ω -3-fatty acids reduce IL-1 β production by suppressing nuclear translocation of NF- κ B and enhancing autophagy [175] and inhibit caspase-1 activity and subsequently, nucleotide-binding domain, leucine-rich repeat-containing family, pyrin domain-containing 3 inflammasome activity [176]. The exact mechanisms of why various fatty acids improve sepsis outcome in animal and patient studies vary; however, both LPC and ω -3-fatty acid supplements were shown to reduce IL-1 β , which can be a key player in severe inflammation during sepsis. Although inflammation is required for clearance of invading pathogens, severe inflammation is associated with a worse outcome of sepsis. Therefore, the capacity of fatty acids to reduce IL-1-mediated inflammation might be a key determinant in explaining their beneficial effect.

HOW DO DIFFERENT PATHOGENS SKEW METABOLISM?

Different microorganisms activate the immune system through different PRRs. TLR4 is one of the main receptors of Gram-negative

bacteria, as a result of its recognition of LPS [177], whereas Gram-positive bacteria activate the host response through other PRRs, such as TLR2 or nucleotide-binding oligomerization domain-containing protein 2. In fungal sepsis, immune recognition is primarily mediated through CLRs, such as dectin-1, dectin-2, or the mannose receptor [178]. The different PRR pathways are specialized to recognize specific pathogens and adapt the immune response to clear the specific pathogen. Therefore, it is unsurprising that as a result of the induction of different intracellular signaling cascades, such as TLR4 through MyD88 and Toll/IL-1R domain-containing adapter-inducing IFN- β and TLR2-only MyD88 and CLRs through caspase recruitment domain family member 9, different pathogens might induce different functional programming in immune cells during sepsis. In line with this, it has been demonstrated that different bacterial pathogens, including *Listeria monocytogenes*, *Bacillus anthracis*, *Mycobacterium tuberculosis*, *Helicobacter pylori*, and *Porphyromonas gingivalis*, induce different epigenetic programs in leukocytes [179], yet how this impacts cellular metabolism was not investigated.

Interestingly, no major differences in the plasma metabolites of patients with sepsis caused by *Streptococcus pneumoniae*, *S. aureus*, or *E. coli* could be found [158]. However, this study did not investigate cellular metabolism of immune cells, in which differences in metabolic status might be present.

Recognition of the fungal cell-wall molecule β -glucan through dectin-1 has been associated with training monocytes to be able to respond more potently to a second stimulus [180, 181]. This reprogramming of monocytes was mediated through induction of mTOR and Hif1 α , leading to increased glycolysis and lactate production, whereas OxPhos and the TCA cycle were down-regulated [17]. Challenge of monocytes with *E. coli* LPS through TLR4, on the other hand, makes monocytes unresponsive to a secondary stimulus [180], similar to what is observed during sepsis-induced immune tolerance. Macrophage exposure to LPS leads to epigenetic reprogramming of the cell that is different than the reprogramming by the fungal molecule β -glucan [180]. As previously mentioned, acute LPS stimulation induces an increase in glycolysis and a decrease of the TCA cycle and OxPhos [19, 20, 55]. Likewise, in a rat *K. pneumonia* sepsis model, glycolysis is stimulated and promoted fatty acids and creatine phosphate oxidation [22]. Yet, in contrast to the LPS-induced Warburg effect, an increase in TCA cycle activity was observed.

Although metabolic changes induced by some microorganisms are known, data comparing metabolic changes between different pathogens are scarce. The studies comparing the fungal cell-wall molecule β -glucan with LPS provide a first insight that metabolic changes could fundamentally differ among various pathogens. However, additional studies containing clinical data and different pathogens are required to elucidate this in detail.

FUTURE PERSPECTIVES

Metabolite assessment for diagnosis and outcome

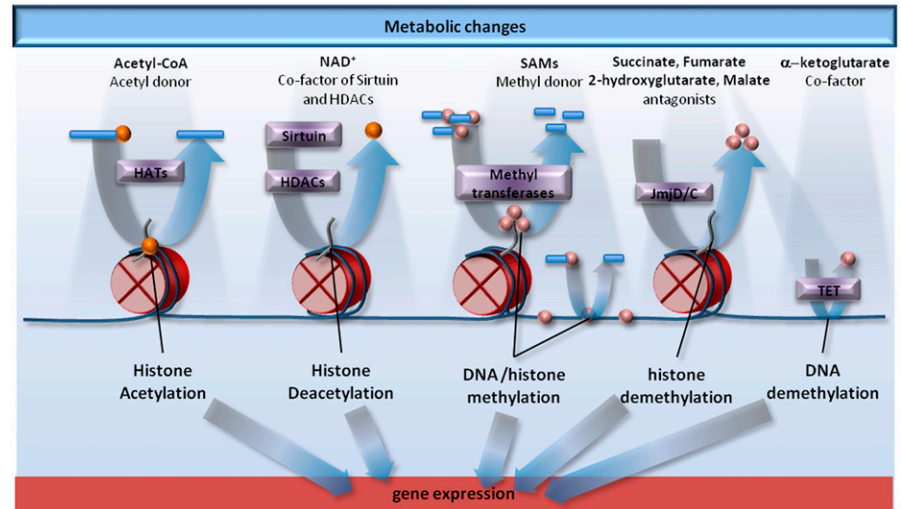
Diagnosis of sepsis and outcome prediction remains difficult. Several biomarkers have been proposed to determine prognosis, but to date, all of them do not reach sufficient sensitivity and

specificity to discriminate on individual patient level [182–184]. With the consideration of the recent views on immunometabolic differences during sepsis, metabolomics was hypothesized to be a valuable approach for diagnosis and prognosis in sepsis patients [158, 185]. Serum used to be the most convenient sample for metabolic assessment, but longer processing times, resulting in higher variability in metabolites, make serum less reliable [185, 186]. Therefore, whole-blood metabolomics was suggested to be a more-promising tool, with more metabolites (in higher concentrations) to be measured and taking erythrocytes into account as well [185]. In a study with >1000 sepsis patients, a metabolomics (and proteomics) analysis on plasma samples revealed differences, especially in fatty acid transport and β -oxidation, gluconeogenesis, and the TCA cycle between the survivors and nonsurvivors group. These differences became even more apparent as the time to death decreased. In the fatty acid metabolism, a clear defect in fatty acid β -oxidation was observed in nonsurvivors, which was absent in survivors [158]. Additionally, glucose metabolism and the TCA differed between survivors and nonsurvivors, with plasma concentrations of citrate, malate, glycerol, glycerol 3-phosphate, phosphate, and glucogenic and ketogenic amino acids decreased in survivors compared with controls. In contrast, the plasma concentrations of citrate, malate, pyruvate, dihydroxyacetone, lactate, phosphate, and gluconeogenic amino acids were increased in nonsurvivors compared with controls [158]. Therefore, the targeting of amino acid metabolic pathways might be a promising therapeutic target and might also serve for diagnosis and prognosis. As current approaches have focused on metabolites in plasma, we suggest that assessment of cellular metabolites from the monocytes that undergo differential metabolic stages during sepsis might have additional predictive value.

REGULATORY ROLES OF METABOLITES

Apart from the direct role of metabolites in insuring the energy resources of the body and as building blocks in the cell, often underestimated is their role in signaling pathways and regulation of gene expression. Recent insights have revealed that a number of metabolites are cofactors for epigenetic enzymes and thus, modify the epigenetic and transcriptional landscape of the cell [187]. We believe that the impact of metabolites on epigenetic mechanisms may represent a crucial path for a better understanding of immunotolerance in sepsis and has a high potential to be targeted for novel therapy. To date, little is known about the interaction of metabolism and epigenetics in sepsis and immunotolerance. However, a few interesting observations have already been made. One of the most extensively described roles is that of the deacetylase enzymes SIRT1 (and especially SIRT1) in sepsis. TLR4 signaling results in SIRT1 binding to NF- κ B RelA/p65 promoter sites of proinflammatory cytokines. SIRT1 deacetylated lysine 310 of RelA/p65 decreases NF- κ B-dependent transcription. Additionally, histone H4 lysine 16 is deacetylated by SIRT1, with therefore reduced transcription. Importantly, SIRT1 binding to promoters is dependent on its cofactor, the metabolite NAD⁺, which is highly induced in acute inflammation. This is of special interest, as NAD⁺ concentrations highly differ between hyperinflammatory and immunotolerant monocytes [24]. Furthermore, SIRT1 also recruits RelB, which is part of the SIRT1 transcription repressor complex [188]. Interestingly, it was

Figure 2. Metabolites regulating epigenetic modifications. Cellular metabolism can influence epigenetic changes. Acetyl-CoA and SAMs can serve as donors for acetyl or methyl groups, respectively. NAD^+ positively regulates SIRT activity. α -Ketoglutarate is a cofactor for TET family DNA demethylases and JmjC and JmjD family histone demethylases, which can be antagonized by succinate, fumarate, 2-hydroxyglutarate, and malate. 2-HG, 2-Hydroxyglutarate; HATs, histone acetyltransferases.



later also shown that the induction of SIRT1 and SIRT6 plays a major role in metabolism rewiring during immunotolerance. Induction of SIRT6 reduced glycolysis, as SIRT6 silences chromatin at Hif-1 α target promoter sites and decreases H3K9Ac at important glycolytic gene sites [24, 189], whereas induction of SIRT1 increased fatty acid β -oxidation via SIRT1-induced interaction and deacetylation of PGC-1 α and - β , which induced expression of fatty acid transporters CD36 and CPT-1 [24, 190].

The important role for activation of NAD^+ -induced SIRT6 for the decreased host defense mechanisms in sepsis is supported by data showing that inhibition of SIRT1 by a specific inhibitor (EX-527) was able to reverse immunotolerance and improve bacterial clearance and therefore, improve outcome [152]. SIRT1 is directly able to deacetylate and inactivate the p65 subunit of NF- κ B. An increase in proinflammatory cytokine production (especially IL-1 β) was observed in SIRT1 knockout mice [191, 192]. Furthermore, several other HDAC inhibitors have profound changes on immunologic end points (reviewed by Ciarlo et al. [193]), which mainly can be summarized by increased susceptibility to bacterial and fungal infections but lower chance of mortality from septic shock [194–197].

In addition, AMPK is activated in sepsis (therefore inhibiting mTOR and Hif1 α), and this has been shown to modulate sepsis-induced lung injury positively and increased the eradication of *Pseudomonas aeruginosa* by reducing the development of endotoxin-induced, tolerant macrophages. Moreover, AMPK activation reduces cytokine production, MAPK activation, and activating transcription factor 3 induction, which results in a less-pronounced immunotolerant phenotype and less organ failure in sepsis [80, 198–200]. AMPK activation also inhibits HMGB1 release, which has a positive effect on survival in murine sepsis models [201–203]. In addition, AMPK has the capacity to improve the blood-brain barrier in murine LPS sepsis, through suppression of NAD(P)H oxidase-derived ROS [204, 205].

The role of epigenetic mechanisms in immunotolerance is relatively well established, with profound changes of histone methylation and acetylation, as well as DNA methylation. Furthermore, as reviewed above, clear metabolic changes during

monocyte and macrophage activation are apparent. Therefore, we hypothesize that the interaction between metabolic pathways and the epigenetic profile of the cell plays a major role in the inflammatory phenotypes of monocytes and macrophages during sepsis. Several roles of metabolites on epigenetics have been described. The role of NAD^+ on SIRT6 and therefore, histone deacetylation has been described above, but also, several other metabolites are known to have major influences on the epigenetic landscape. Acetyl-CoA is a direct acetyl donor for histone acetylation, and the rate of glycolysis was directly associated with the acetylation of specific histone sites, which appeared to be mostly dependent on acetyl-CoA levels [206]. Furthermore, the TCA metabolite α -ketoglutarate is an essential cofactor for histone demethylases (JmjC and JmjD) and TET enzymes, which regulate DNA methylation. Molecular comparable metabolites, such as succinate, fumarate, malate, and 2-hydroxyglutarate, can antagonize this reaction [207, 208] (Fig. 2).

SAM, which is derived from folic acid and methionine metabolism, affects histone and DNA methylation, as it serves as a methyl donor for histone and DNA methyltransferases [209] (Fig. 2). All of these regulating mechanisms of metabolites on epigenetic modifiers can potentially influence the phenotype of monocytes and macrophages during sepsis [158, 210]. During the development of monocyte to macrophage, it has already been shown that metabolic changes are also partially the result of epigenetic changes [17, 180], so the effects of metabolism on epigenetics and vice versa are most likely a complex interaction, in which both influence the each other. It is proposed that metabolic–epigenetics interaction is a field that should be the focus of future research, on the one hand for diagnostic and prognostic markers but on the other hand, also for novel therapeutic approaches (Fig. 3).

POTENTIAL THERAPEUTIC STRATEGIES

Most of the potential immune-based treatments in sepsis are directed to inhibit the acute and hyperinflammatory state of sepsis. However, most of the sepsis patients have already past this phase

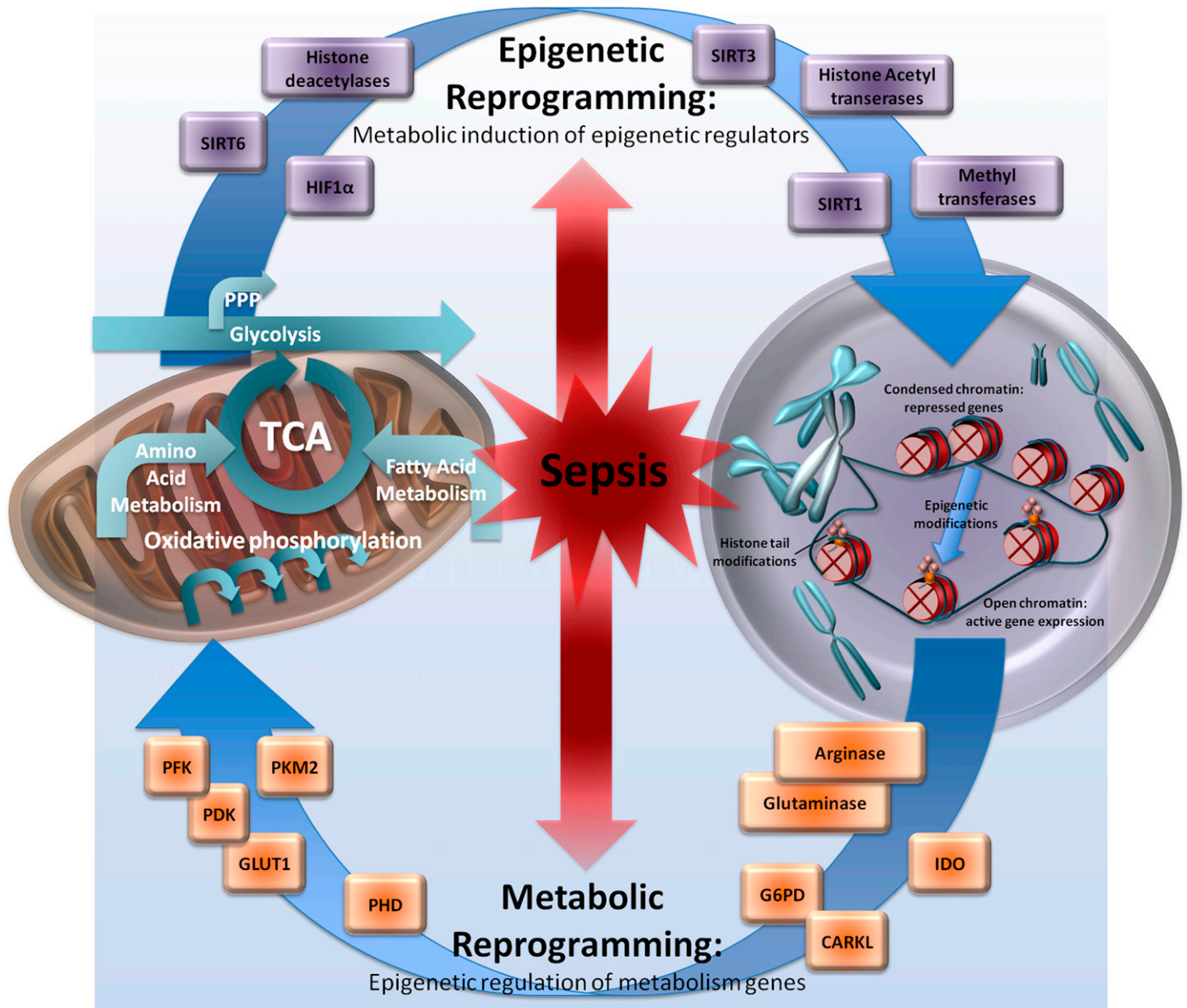


Figure 3. The impact of metabolic pathways on the epigenetic landscape. Sepsis induces metabolic and epigenetic reprogramming. Metabolic changes can influence epigenetic modulators that modify gene expression by condensing or opening chromatin. Alternatively, epigenetic changes regulate the expression of metabolic genes that modulate cellular metabolism.

upon diagnosis, or simultaneously, their cells are progressing toward an immunotolerant state. Therefore, therapies directed toward the immunotolerant state of sepsis are more urgently needed, of which, to date, only very few therapies are available. In this regard, EX-527, a SIRT1 inhibitor, is able to shift tolerant monocytes toward a more proinflammatory phenotype, which promisingly resulted in 100% survival when administered 24 h after induction of sepsis by CLP in mice compared with 40% in the control group. Moreover, EX-527 at earlier time points significantly increased mortality [24, 152]. Administration of IFN- γ improved cytokine production and glycolysis, both in vitro and in vivo in human fungal sepsis [5, 47, 48]. However, further studies on defects in metabolism during the immunotolerant state of

sepsis and how these defects potentially could be reversed are therefore warranted.

CONCLUDING REMARKS

In this review, we illustrate that during sepsis, major changes in cellular metabolism take place. Different metabolic states are associated with different immunologic states of sepsis. The use of metabolomics for diagnosis and prognosis is a fairly novel field of research but shows encouraging results. In addition, the interaction between the metabolic profile and the epigenetic landscape is a new and promising field for development of novel therapies directed to improve immune responses in infections and sepsis.

AUTHORSHIP

R.J.W.A. and M.S.G. did the literature search. R.J.W.A., M.S.G., L.A.B.J., and M.G.N. wrote the paper.

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DISCLOSURES

The authors declare no conflicts of interest.

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Cellular metabolism of myeloid cells in sepsis

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