Metabolic reprogramming consequences of sepsis: adaptations and contradictions

Jingjing Liu1 · Gaosheng Zhou1 · Xiaoting Wang1 · Dawei Liu1

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Abstract
During sepsis, the importance of alterations in cell metabolism is underappreciated. The cellular metabolism, which has a variable metabolic profile in different cells and disease stages, is largely responsible for the immune imbalance and organ failure associated with sepsis. Metabolic reprogramming, in which glycolysis replaces OXPHOS as the main energy-producing pathway, is both a requirement for immune cell activation and a cause of immunosuppression. Meanwhile, the metabolites produced by OXPHOS and glycolysis can act as signaling molecules to control the immune response during sepsis. Sepsis-induced "energy shortage" leads to stagnated cell function and even organ dysfunction. Metabolic reprogramming can alleviate the energy crisis to some extent, enhance host tolerance to maintain cell survival functions, and ultimately increase the adaptation of cells during sepsis. However, a switch from glycolysis to OXPHOS is essential for restoring cell function. This review summarized the crosstalk between metabolic reprogramming and immune cell activity as well as organ function during sepsis, discussed the benefits and drawbacks of metabolic reprogramming to show the contradictions of metabolic reprogramming during sepsis, and assessed the feasibility of treating sepsis through targeted metabolism. Using metabolic reprogramming to achieve metabolic homeostasis could be a viable therapy option for sepsis.

Keywords Sepsis · Metabolic reprogramming · Immunosuppression · MODS · Tolerance · OXPHOS · Glycolysis

Introduction
Sepsis is a serious life-threatening disease in the ICU, with at least 19 million patients reported worldwide each year [1, 2]. In general, a strong pro-inflammatory effect eliminates the pathogen in the early stages of inflammation, and the immune system progressively shifts to an anti-inflammatory state as the disease progresses, mostly to minimize inflammation and promote tissue healing. The balance between pro- and anti-inflammatory is an essential component of the normal functioning of the body’s immune system. However, during sepsis, the disrupted pro- and anti-inflammatory balance typically results in inflammatory storms and immunosuppression, which lead to excessive cellular damage and inability to respond to secondary infections, ultimately causing fatal multi-organ dysfunction syndrome (MODS). MODS is the most serious complication of sepsis, but its pathogenesis is still poorly understood. Severe immunosuppression and MODS create a therapeutic dilemma in sepsis, despite decades of research by researchers, there have been no significant breakthroughs in treatment, which is still dominated by antibiotics and organ support. The dynamics of cellular energy metabolism, the basis of cellular activity during sepsis, is a role that cannot be ignored.

Metabolic reprogramming occurs in almost all types of cells during sepsis. Immune cells undergo tumor-like changes—the "Warburg effect" [3–6], where cells switch to glycolysis as their primary source of energy instead of oxidative phosphorylation (OXPHOS) under aerobic conditions, which is critical to immune cell activity during sepsis. The reprogramming that glycolysis replaces OXPHOS...
is also observed in organ cells, such as tubular epithelial cells (TECs) [7] and cardiomyocytes [8]. Singer et al. [9–11] have argued that sepsis-induced MODS may represent a defensive strategy for the host in response to metabolic dysregulation and insufficient energy, which links the vital and functional activities of organ cells to metabolic reprogramming. Furthermore, the relevance of metabolic reprogramming to sepsis was highlighted again by Raymond et al. [12] in 2013, who found that the metabolomes and proteomes of patients at the hospital who would ultimately die differed markedly from those of patients who would survive. Sepsis is a disease with a complicated metabolism, and the significance of metabolic reprogramming in sepsis requires more exploration. Identifying the crosstalk between metabolism and disease is essential for the diagnosis and treatment of sepsis. Moreover, as the concept that the oxygen delivered to the cells is sufficient is gradually recognized, “cytopathic hypoxia” caused by mitochondrial dysfunction or changes in metabolic enzyme activity may be a better explanation for metabolic reprogramming.

This review aims to describe alterations in oxidative metabolism and glycolysis in immune and organ cells during sepsis and to summarize their interrelation with cellular function. We emphasized the importance and complexity of metabolic reprogramming in sepsis, as well as suggested to maintain metabolic homeostasis may be a strategy for the future treatment of sepsis. At the same time, the key role of mitochondria as a metabolic organelle in sepsis metabolism regulation will also be underlined.

**Glycolysis is a double-edged sword for the immune system during sepsis**

Energy metabolism in cells is driven mainly by OXPHOS and glycolysis. Since the study in the 1950s demonstrated that lymphocyte activation was associated with an increase in glucose consumption [13], the key role of metabolism in the activation, proliferation, and differentiation of immune cells has been gradually identified [14] and evidenced by studies of tumors [15] and diabetes [16, 17]. Immune dysfunction is one of the most prominent clinical features of sepsis. Knowledge of the effects of metabolism on immune function will help to elucidate the imbalance between the pro-inflammatory and anti-inflammatory.

**Metabolic reprogramming of immune cells during sepsis**

Innate immune cells (monocytes, macrophages, granulocytes, natural killer cells, and dendritic cells), adaptive immune cells (lymphocytes), and certain vascular cells (endothelial cells and vascular smooth muscle cells) all play roles in the inflammatory response. The innate immune cells recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through surface receptors (Toll-like receptors (TLRs) and c-type lectin receptors (CLRs)), cytoplasmic receptors (nucleotide-binding oligomerization domain (Nod)-rich leucine repeat receptors (NLRs) and RIG-I-like receptors (RLRs)) [18] to release signaling and effector molecules to trigger inflammatory responses and kill invading microbes, as well as mobilize adaptive immune cells (T lymphocytes and B lymphocytes) to generate delayed but stronger and more specific immune responses. During the activation of immune cells, the energy metabolic pathway is reprogrammed from OXPHOS to glycolysis.

Although resting dendritic cells (DCs) are dependent on mitochondrial OXPHOS fuelled by the β-oxidation of lipids [19–21], metabolic reprogramming from OXPHOS to glycolysis triggered by TLR signaling is essential for DC maturation and associated biologic functions [21]. When glycolysis is blocked with the glycolytic inhibitor 2-DG [6], DCs activation is considerably reduced with the release of IL-6 and TNF substantially impaired [6, 21]. Similar to DCs, mature neutrophils’ glycolysis is associated with their metastatic activity [22] and the creation of neutrophil extracellular networks (NETs), which kill bacteria after metastasis to the target region [23]. Macrophages are induced into M1-or M2-type after being activated by LPS. The differentiation between M1- and M2-type macrophages plays the opposite role in sepsis. Porta et al. [24] and Pena’s team [25] have illustrated that M1-type macrophages are responsible for secreting pro-inflammatory factors and promoting inflammation, and M2-type macrophages are responsible for reducing inflammation and repairing damaged tissues. In the resting state, macrophages create energy mostly by OXPHOS [26, 27], whereas M2-type macrophages primarily utilize fatty acid oxidation (FAO) to support the anti-inflammatory function and M1-type macrophages mainly use glycolysis not only for faster ATP production but also to obtain the biosynthetic raw material [28].

OXPHOS provides energy to immature T cells, whereas activated effector T lymphocytes switch to glycolysis to speed up ATP production [29–31]. Different T cell subsets, however, have different metabolic properties. For instance, effector T cells (Teffs) that dominate the pro-inflammatory response, such as Th1, Th2, and Th17 [29], mainly rely on glycolysis, whereas regulatory T-cells (Tregs) and memory T cells (Tmems) which mainly play an anti-inflammatory role mostly use fatty acids in their metabolism, and mTORC1 activation drives Teff cells differentiation while suppressing Treg cells [32–34]. However, some research has found that sped Treg cell proliferation by Ethyl Pyruvate has been connected to glycolysis rather than OXPHOS [31].
Metabolic reprogramming mainly involves suppressed mitochondrial oxidative function and an increased glycolytic capacity. LPS causes increased glycolysis while inhibiting mitochondrial respiration by suppressing nitrosylation of cytochrome C oxidase and complex enzyme I in the electron transport chain [27, 35]. The mTOR-HIF-1α pathway is also activated in macrophages by LPS, which prompts increased expression of HIF-1α downstream glycolytic enzymes like glucose transporter protein 1 (GLUT1), fructose-2,6-bisphosphatase 3 (PFKFB3), hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), and lactate dehydrogenase (LDH) to elevate glycolytic capacity [36]. AMPK promotes β-oxidation of fatty acids by regulating proliferator-activated receptor γ (PPAR-γ) and carnitine palmitoyl transferase 1 (CPT1), but in sepsis, the downregulated AMPK pathway promotes the glycolytic capacity of macrophages [37, 38] and directly affects the secretion of inflammatory and anti-inflammatory factors like IL-1β and IL-6.

Enhanced glycolysis contributes to immune cell activity

The "Warburg effect" is favorable because of its ability to provide not only ATP but also metabolites that contribute to the activities of the immune cells [39]. The increased expression of GLUT1 during sepsis promotes the competitive uptake of glucose [40, 41], a source of carbon that can be used for biosynthetic in addition to being a source of energy [42]. When GLUT1 expression is depressed, glucose uptake and glycolysis are significantly inhibited, along with a significant decrease in T eff's vital and functional activities [29, 40]. On the other hand, the increased glucose uptake and glycolytic flux, as well as the high rate of ATP production by glycolysis, allow ATP from glycolysis to meet the energy requirements of activated immune cells, even when OXPHOS is inhibited. The glucose 6-phosphate (G-6-P) produced in the first phase of glycolysis can be imported into the pentose phosphate pathway (PPP) to nucleotide synthesis, while the NADPH produced is a cofactor necessary for a variety of metabolic processes, such as lipid synthesis [43]. Dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (G-3-P) from glycolysis are the raw materials for lipid synthesis and amino acid synthesis, respectively [44]. In addition, citrate is converted to cytoplasmic acetyl coenzyme A in the tricarboxylic acid (TCA) cycle, which is used to make cholesterol and fatty acids for lipid synthesis [45]. Glycolysis offers the biological raw materials that immune cells require for proliferation and synthesis.

Glycolysis provides enough energy and biomolecules to activate the immune system, allowing for a more efficient and quick immune response. In this way, limiting glycolysis appears to lessen the inflammatory storm [46, 47]. Hannah R et al. [48] have determined in bovine heart mitochondria that metformin directly inhibits complex I activity in a non-competitive manner and ATP synthase activity, which in turn leads to a decrease in OXPHOS and activation of AMPK in cells [49, 50], which support metformin to reduce macrophage NLRP3 inflammasome in diabetes [51, 52]. However, in 2021, Hongxu Xian et al. [53] found that independent of AMPK or NF-κB pathways, metformin blocked LPS-induced ATP-dependent synthesis of the NLRP3 ligand mtDNA and ultimately affected interleukin (IL-1) production, while metformin may also affect inflammasome non-dependent IL-6 secretion via JNK and p38-MAPK activation, thereby attenuating LPS and SARS-CoV-2-induced ARDS. Similarly in LPS-stimulated BMDMs, metformin, without AMPK activation, decreased LPS-induced production of the pro-IL-1β at both the mRNA and protein levels and boosted LPS induction of the anti-inflammatory cytokine IL-10 [54]. ROS also has been reported involved in LPS-induced IL-1β mRNA production [55]; both metformin and rotenone influence IL-1β production by affecting ROS production of mitochondrial complex I [56]. mTOR is a central regulator of cellular metabolism, and targeting mTOR with rapamycin or derivatives thereof will generally activate downstream molecules such as HIF-1α [57] and GLUT1 [58] to promote glucose uptake and glycolysis [57]. Further, LPS-induced pro-IL-1β and subsequent ATP-induced IL-1β release were cut off by the rapamycin [59]. In CD8+ T cells, blockade of mTOR by rapamycin also promoted the differentiation of Tmem cells [60, 61], which may ultimately provide us with a novel therapeutic target for altering the course of immune disorders and inflammation.

An excessive level of glycolysis causes immunosuppression

The glycolysis supports the rapid activation of immune cells to release large amounts of pro-inflammatory factors and even cause "inflammatory storms," which are extremely prone to excessive cellular damage. Most patients can survive "inflammatory storms" but get worse due to immunosuppression. Immunosuppression is often manifested by reduced expression of genes encoding pro-inflammatory cytokines and chemokines that recruit T cells (e.g. TNF-α, IL-6, CCL2) but increased expression of anti-inflammatory cytokines (e.g. IL-4, IL-10) [62, 63], which means that the host is unable to respond effectively to the "secondary infection." This transition from "inflammatory storms" to hypo-inflammation is accompanied by a shift in the substrate utilization of immune cells from glucose to fatty acid oxidation. The human sepsis blood leukocytes have shown increased fatty acid transporters (eg. CD36) and CPT-1 levels during the immunosuppressed stage [64]. Divya Vats et al. [65] have shown that IL-4-mediated activation of STAT6 in macrophages induces...
uptake and oxidation of fatty acids as well as biogenesis, and PGC-1β knockdown decreases FAO while increasing the pro-inflammatory effector properties of macrophages. SIRT1 and SIRT6 link metabolism with the early and late stages of acute inflammation responses by supporting the switch from glycolysis to FAO [64]. In addition to FAO promoting the anti-inflammatory phenotype in immune cells, lactate produced by glycolysis during the pro-inflammatory phase also exerts a potent immunosuppressive effect.

Lactate’s role in the clinical treatment of sepsis is undeniable, but it is far from being a simple metabolite, and more studies are identifying lactate as an active signaling molecule [66, 67], such as Lactate-GPR81 [68, 69] and Lactate-GPR132 signaling axis [70]. Particularly the functions of dynamic regulation and balance to histone lactation modifications and inflammation-related gene expression [71–73] give lactate a new identity in the regulation of immune function.

Zhang et al. [74] found that elevated intracellular lactate inhibits cytoplasmic RLRs-mediated activation of IFNs on M1-type cells. Also during macrophage cytosolic emesis, lactate increases the expression of anti-inflammatory genes Tgfβ and IL-10 as well as M2-type genes Vegfa, Mgl1, and CD206 in nearby immune cells via paracrine secretion, which in turn promotes an anti-inflammatory milieu [75]. High levels of lactate also support the expression of the M2-type macrophage homeostatic genes Mrc1 and Arg1 to promote the M2-type macrophage development but suppress M1-type macrophages [76]. Similarly, lactate inhibits the inflammatory response and promotes the polarization of M2-type macrophages through GPR81-dependent antagonism of TLR4-mediated signaling pathways and consequently attenuated LPS-induced NF-κB activation [68, 69, 77–79]. High levels of lactate inhibit the differentiation of monocytes into DCs and hamper DCs formation and accumulation [80, 81].

When lactate is transported outside the cell via the monocarboxylate transporter protein MCT4, it modulates migration and cytokine production of immune cells in various ways and induces a "stop migration" signal mediated by the lactate transporters SLC5A12 (CD4 T cells) and SLC16A1 (CD8 T cells) [82]. These inhibitions of T-cells function and apoptosis are coupled with decreased expression of several glycolytic enzymes and glucose flux, such as downregulation of PFKFB3 leading to G-6-P toward the PPP [28, 83]. Lactate efflux causes acidification of the extracellular environment, which induces an incompetent state of CD8+ T cells with reduced cytolytic activity and cytokine secretion when the pH is between 6.0 and 6.5, and also causes immune cell death, whereas proton pump inhibitor treatment effectively restores T cell function [28]. MCT1/MCT4, lactate transporters into and out of cells, have emerged as new targets for tumor therapy [84–86], while there were few studies in sepsis. The effect of MCT1 or MCT4 on immunosuppression in sepsis is worthy of more study.

Metabolic reprogramming of immune cells to glycolysis during sepsis is an essential component of the initiation of the host defense response. Whether glycolysis is a passive choice due to the inhibition of OXPHOS or an active selection of immune cells, its role in the pro-inflammatory reaction is crucial. At the same time, the lactate produced by glycolysis feedback promotes the anti-inflammatory response, which is helpful to maintain immune homeostasis. However high-level lactate will cause immune suppression by promoting immune cell death or inactivation, which disrupts the immune homeostasis of the body. Figure 1 shows the cross-talk between metabolic reprogramming and the activities of immune cells. Cellular self-regulation is very clever and fine, and controlling immune cell metabolism at the right time is a crucial strategy for maintaining immunological homeostasis. Once a wide range of immune cells has been activated, how to modulate the degree of glycolysis at the right time to restrict the inflammatory response while avoiding the immunosuppression induced by excessive lactate is what future research should focus on.

Metabolic reprogramming is a cell adaptability mechanism but also causes MODS

After Hotchkiss et al. [87] in 1999 demonstrated that cell death cannot explain the development of organ dysfunction during sepsis, Takasu et al. [88] also discovered that cardiomyocytes and kidney cells from sepsis-dead patients did not show necrosis or apoptosis in 2013, which means that sepsis-induced MODS may have other underlying mechanisms. A recent study found that mitochondrial DNA was broken and mitochondrial homeostasis-related genes were down-regulated in kidney biopsy samples from dead SAKI patients [89], and more and more studies have linked mitochondrial dysfunction to sepsis. A bold prediction appears plausible—energy shortage linked with impaired mitochondrial function in sepsis may be a crucial component contributing to MODS.

Tolerance: a new way to understand MODS

In 2008, a defense present in plants that reduces the negative effects of infection was also found in animals—tolerance [90, 91]. The discovery has opened up new areas of research into pathogen–host relationships and provided new perspectives for the understanding of sepsis-induced MODS. Even in adverse conditions, tolerance offers cells the opportunity
to survive even at the expense of their functional activity, i.e., "where there is life, there is hope."

In the long evolutionary process of life, limited resources are utilized for the body's life preservation, growth, and reproduction, and wise energy allocation is necessary. A host can evolve two types of defense mechanisms to increase its fitness when challenged with a pathogen resistance, which drives the immune to clear the pathogens, and tolerance, which reduces infection impact on health in other ways.

The requirement of a large amount of energy in the resistance process during sepsis leads to energy competition in the host, especially in the case of decreased ATP due to mitochondrial damage or hypoxia [92, 93]. The host needs to make an energy trade-off between resistance (mobilizing immune cells) and tolerance (maintaining organ function) and ultimately prioritizes the needs of immune cells [94]. Kirthana et al. [95] demonstrated that activation of immunity by LPS finally triggered energy conservation, and the energy trade-off between immunity and homeothermy triggers entry into a hypometabolic–hypothermic state that enhances tissue tolerance. Kirthana et al. [95] also thought tissue tolerance is the mechanism of hibernation. Hypothermia–hypometabolism have been shown to enhance survival in acute sickness in both animal and human studies [96, 97]. Sepsis-induced MODS is characterized by minimal cell death, reduced cellular oxygen consumption, and normal/elevated tissue oxygen levels [9]. In addition, in survivors, organs usually return to function within days to weeks [98]. So Singer et al. [10] hold that MODS may be a hibernation phenomenon due to adaptive shutdown aimed at reducing cellular energy requirements, with a trade-off between organ function and cellular viability. Miguel et al. [99] have also proposed that tolerance is a defense strategy to maintain the health of the body by limiting organ damage.

Driving immunity to clear pathogens is an energy-intensive process, which means that less energy is available to organ cells; a reasonable energy distribution is also required between the vital and functional activities of the
cells to ensure cells’ survival. When turtle liver cells were exposed to hypoxia, researchers noticed that cellular energy and oxygen consumption dropped, but that critical activities including intracellular ion balance were intact [100]. Cell function was likewise stopped in a model of induced hibernation in rat hepatocytes, but Na⁺/K⁺ ATPase activity was maintained, and hepatocytes restored oxygen consumption and ATP generation to normal oxidation after reoxygenation capability [101].

Tolerance reflects the flexibility of cells to balance their survival and function, and energy allocation is an important manifestation of tolerance. The correlation between tolerance, energy trade-offs, and MODS highlights the central role of energy in sepsis and also implies an impact of metabolic reprogramming on organ cell function.

The metabolic reprogramming is a key indicator of tolerance.

The overarching principles and mechanisms that control the expression of tissue tolerance programs remain largely unclear, but there is no doubt that energy is an important factor in tolerance. We all know that infected animals’ metabolism skews toward FAO for ATP, accompanied by increased levels of free fatty acids in the blood. A study by Khan et al. [102] showed that the level of cellular lipid metabolites deviates from a “safe range” when comparing plasma lipid metabolism profiles between septic and non-septic patients and that the level of lipid metabolites is related to sepsis mortality. FAO is primarily controlled by PPAR-α (encoded by the NR1C1 gene), and several studies have reported decreased PPAR-α levels in the organs and whole blood during sepsis. The rapid decline of hepatic PPAR-α levels causes excess free fatty acids, and PPAR-α agonist pemafibrate protects against lipotoxicity and tissue damage by improving hepatic PPAR-α function in sepsis [103]. Takuma et al. [104] demonstrated that mice lacking PPAR-α had poor renal functions and that diminished PPAR-α signaling increased the incidence of AKI. Drosatos et al. [105] also found that JNK inhibition prevented LPS-mediated cardiac dysfunction by increasing PPAR-α expression to improve FAO.

Although the sepsis-induced “starvation response” promotes FAO to be considered the primary energy supplier, there is still a suppression of FAO during sepsis, and the oxygen and the normal function of mitochondria for ATP are difficult to achieve during sepsis, so FAO is not the best way to enhance tolerance. Glycolysis, not required mitochondria and oxygen, becomes the main candidate for increased tolerance during sepsis. Recent studies suggest that metabolic adaptations to bacterial infections are a critical determinant of tissue tolerance [94, 106]. As previously indicated, the “Warburg effect” is used in the process of immune cell activation to maintain energy requirements and support biosynthetic chemicals, as well as to create a memory for a specific insult and modulate the response to future insults (a process known as trained immunity) [57]. Katherine et al. [106] found that glycolysis manipulation alters the disease tolerance of mice suffering from malaria, and supplemental glucose improves survival by promoting glycolysis.

Glycolysis during sepsis is the main pathway that determines the allocation of energy to organ cells, and changes in glycolysis reflect the activation and strength of cellular tolerance. It is reasonable to assume that the reprogramming from OXPHOS to glycolysis is a protective mechanism that maintains the cellular survival state by enhancing cellular tolerance and reducing cellular damage. During sepsis, both glucose uptake and the expression of glycolysis-related enzymes were significantly altered in organ cells. Sepsis elevates glucose uptake and the expression of GLUT1 protein 1.7-fold in the skeletal muscle of septic rats to enhance glycolysis [107]. In LPS-induced pulmonary fibrosis, LPS causes lung fibroblast aerobic glycolysis through the activation of the PI3K-Akt-mTOR/PFKFB3 pathway [108]. LPS also activates key molecules that regulate metabolisms such as HIF-1α [109] and AMPK [110]. These reprogramming of OXPHOS to glycolysis may be a pre-determined defense mechanism.

Metabolic reprogramming may also be the result of mitochondrial dysfunction or hypoxia. However, it is undeniable that glycolysis alleviates the energy crisis and promotes the tolerance of cells in harsh environments. The shift to glycolysis of cardiomyocytes to survive ischemia and hypoxia is thought to be an energy compensatory mechanism [111], and Singer et al. [10] also suggested that sepsis-induced low cardiac output is a “hibernation”-like phenomenon exhibited by the myocardium in the presence of energy deficit. Cells re-prioritize energy expenditure to maintain vital activities at the expense of organ function in low-energy situations, and the decrease in cellular function may be a protective mechanism facing inadequate energy production. At this point, the more energy produced by glycolysis, the stronger tolerance, and the more survival organ cells.

Switching back from glycolysis to OXPHOS is essential for MODS

Although switching to glycolysis enhances the tolerance to ensure cell survival for a short period and effectively avoids re-injury to mitochondria and cells by ROS, as well as downstream adverse reactions caused by ROS are suppressed, long-term glycolysis is damaging to organ function cells. Exogenous lactate caused an increase in mitochondrial damage in HK2 cells after 6 h, and cell survival was severely reduced after 24 h [112]. Long-term glycolysis has been reported to cause permanent renal shrinkage and fibrosis in
TECs, increasing the probability of transitioning from AKI to chronic kidney disease [7]. By quickly reverting OXPHOS to an energy supply mode, the prognosis of sepsis can be greatly improved. For example, Shikonin, a powerful PKM2 inhibitor, reduces serum lactate and HMGB1 levels to protect mice from sepsis [113]. The activation of SIRT1, an important facilitator protein of OXPHOS, can enhance the survival of sepsis mice, according to Opal et al. [114] and Vidula et al. [115]. Treatment with the glycolysis inhibitor 2-DG enhanced heart function and survival outcomes in a mouse model of septic cardiomyopathy [8]. Although glycolysis may help cells survive in the early stages of sepsis, it is clear that a return to OXPHOS metabolism is necessary, especially for those relying on OXPHOS.

The strength of tolerance can alter the outcome of cells in adverse situations. Lives evolve under survival pressure, and timely trade-offs are a crucial approach to adapting to the rule of superiority and inferiority. Cell evolution has resulted in a collaboration between OXPHOS and glycolysis for energy supply. When OXPHOS is disrupted, the small amount of ATP produced by glycolysis is mainly used to sustain life activities, and the restoration of OXPHOS is necessary for the recovery of cellular function. Tolerance offers us a unique perspective on MODS. As shown in Fig. 2, metabolic reprogramming promotes tissue tolerance to protect organ cells during sepsis.

Mitochondria are essential to the metabolism of sepsis

It is vital to re-establish the function of OXPHOS in immune cells as well as organ cells. The operation of OXPHOS requires a healthy inner mitochondrial membrane and flawless mitochondrial activity, so the contribution of mitochondria to metabolic reprogramming during sepsis cannot be ignored.

Factors affecting mitochondrial function in sepsis

Mitochondrial function is affected during sepsis mainly through several aspects, as shown in Table 1. First, sufficient oxygen is a prerequisite for mitochondrial ATP synthesis. Although the idea that tissue hypoxia is caused by insufficient oxygen delivery during sepsis is gradually being questioned, the mismatch between macrocirculation and microcirculation [116, 117], abnormal volume distribution, and decreased cardiac function [118] during sepsis may all contribute to insufficient tissue oxygen delivery. Even if the various enzyme activity involved in oxygen oxidation are tolerable, ATP cannot be effectively generated under low oxygen levels. When ATP generation falls below a certain level, the apoptotic and necrotic pathway is triggered [119, 120]. Pyruvate dehydrogenase complex (PDC) is the major metabolic enzyme for mitochondrial oxidative energy production, hence, a decrease in its activity will have an immediate influence on mitochondrial energy production. Additionally, PDC is also a bifurcation point between OXPHOS and glycolysis, and its role in metabolic reprogramming cannot be ignored. During sepsis, PDC activity is regulated by HIF-1α [121], glucocorticoid receptor (GR) [122], and peroxisome proliferator-activated receptor (PPAR-α) [123, 124] pathways, which have direct impacts on OXPHOS capability. Meanwhile, the large amounts of NO [125, 126], H₂S [127], ROS [128], and other reactive substances that are produced during inflammation can inhibit the mitochondria function by suppressing ETC complexes and the TCA cycle. Mitochondrial homeostasis (biogenesis, fusion, autophagy) plays a decisive role in the regulation of cellular energy metabolism and signaling pathways. Genes related to mitochondrial biosyntheses, such as peroxisome proliferator-activated receptor-gamma coactivator-1 (PGC-1), mitochondrial transcription factor (Tfam), and nuclear respiratory factor-1 (NRF-1), are also explicitly and significantly repressed [129], whereas increased PGC-1 contributes to organ function recovery [130]. FUNDC1 interacts with LC3 to regulate mitochondrial homeostasis [131], and Ripk3 induces mitochondrial apoptosis via inhibition of FUNDC1 mitophagy [132]. AMPK as the key player in metabolism focuses on the regulation of various aspects of mitochondrial homeostasis [133] and promotes the interaction between mitochondrial fission and autophagy through the regulation of Drp1, Mff, PINK, and Parkin [134]. Uncoupling protein 2 (UCP2) is thought to dissipate the proton gradient across the inner membrane and uncouple the respiratory chain from ATP generation [135]. During sepsis, calcium/calmodulin-dependent protein kinase(CaMK)-IV shifts the balance toward mitochondrial fission and away from fusion by directly phosphorylating fission protein Drp1 and reducing the expression of the fusion proteins Mfn1/2 and OPA1 [136]. CaMK-IV also is a direct PINK1 kinase and regulator of Parkin expression to control mitophagy [136]. Also, stress response during the early stages of sepsis promotes massive hormone secretion [137–140], which to some extent affects mitochondrial function. Thyroid hormones can increase mitochondrial biosynthesis [141, 142] and regulate mitochondrial autophagy [143]. Insulin resistance in type 2 diabetes is closely related to mitochondrial function [144, 145]. Kitada et al. [146] found that SIRT1 also can improve insulin resistance by promoting fatty acid oxidation and mitochondrial biogenesis via deacetylation of PGC-1α and PPAR-α activation in skeletal muscle.
Fig. 2 Metabolic reprogramming promotes tissue tolerance to increase organ cell adaptation during sepsis. Under normal conditions, cells obtain ATP from OXPHOS and glycolysis. Resting immune cells have fewer energy requirements and therefore most of the energy is allocated to organ cells to support functional activities. In sepsis, ATP is preferentially allocated to immune cells to support immune activation for clearing the pathogens, which results in less ATP for organ cells. To reduce energy consumption, organ cells shut down functional activities and use ATP as much as possible to maintain cell life activities, which leads to stagnation in organ cell function even MODS. This is an adaptation mechanism of the host during sepsis. When OXPHOS is suppressed, enhanced glycolysis rapidly supplies ATP to maintain cellular survival and encourages stronger tissue tolerance to adapt to sepsis more easily. It also provides an opportunity for cells to restore OXPHOS to promote recovery of cellular function. GLUT1 glucose transporter protein 1, PFKFB3 fructose-2,6-bisphosphatase 3, HK2 hexokinase 2, PKM2 pyruvate kinase M2, LDH lactate dehydrogenase, Glu-6-P glucose 6-phosphate, Fru-6-P Fructose 6-phosphate, MODS multi-organ dysfunction syndrome.
Treatment of sepsis requires proper mitochondrial function

Mitochondria have long been thought to have functions in the progression of the disease by regulating cell metabolism and influencing ATP production. It is also responsible for a wide range of cellular functions, such as cellular calcium homeostasis and programmed cell death.

Mitochondrial free radicals and ROS can disrupt cell signaling, while the mitochondria themselves are the main targets of ROS damage. UCP2 is a mitochondrial membrane protein that reduces mitochondrial ROS generation by triggering proton leak and thereby lowers mitochondrial ROS production [135]. In a study of septic cardiomyopathy, inhibiting UCP2 enhanced ROS, mitochondrial swelling, and cardiac damage [147], whereas overexpressing UCP2 increased caspase3 activity and Bax protein accumulation, and attenuated cardiomyocyte apoptosis [148]. Upregulation of SIRT3-mediated inhibition of oxidative stress preserved mitochondrial function and induced autophagy in small intestinal epithelial cells, which partially alleviated sepsis-induced small intestinal injury [149]. Suppressed PGC-1α by LPS triggers the reprogramming of cardiac energy metabolism, which is associated with decreased ventricular function in septic cardiomyopathy [150]. At the same time, the mitochondrial homeostasis, including the dynamic process of mitochondrial fusion/fission (Mfn2, OPA1, Drp1), mitochondrial biogenesis (NRF-1, PGC-1α, Tfam), and mitochondrial mitophagy (Parkin, PINK1), protects the lung [136] and kidneys [136] from ongoing oxidative injury [151].

Mitochondria also play a role in modulating immune cell function [152]. TLRs enhanced by mitochondrial ROS allow macrophages to receive and conduct signals more sensitively, improving immune cells' ability to clear harmful bacteria [153]. Secondly, mitochondria-specific protein, mitochondrial antiviral signaling protein (MAVS), accumulates on the surface of mitochondria to serve as a signaling platform to participate in the anti-RNA virus RLR pathway [74, 154]. At the same time, mitochondrial DAMPs, such as

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Table 1 Factors affecting mitochondrial function during sepsis

| Classification                  | Factors                  | Effect on mitochondria | References |
|---------------------------------|--------------------------|------------------------|------------|
| Relative hypoxia                | Macrocirculation         | Oxygen delivery         | De Backer et al. [116] Lin et al. [118] |
|                                 | Cardiac function          |                        |            |
|                                 | Vascular tone             |                        |            |
| Microcirculatory                | Glycocalyx degradation    | O₂ diffusion distance   | De Backer et al. [116] Inkinen et al. [117] |
|                                 | Endothelial dysfunction   |                        |            |
| Oxygen utilization disorder     | Mitochondrial homeostasis| Biogenesis              | Mao et al. [129] Tran et al. [130] |
|                                 | PGC-1α, Tfam, NRF1        | Fusion                 | Seabright et al. [134] |
|                                 | Drp1, Mff                 | Fission                | Zhang et al. [136] |
|                                 | Mfn1/2, OPA1              | Fusion                 |            |
|                                 | PINK, Parkin, FUNDC1      | Autophagy               | Zhang et al. [131] |
| Regulatory molecules            | HIF-1α, GR, PPAR-α        | PDC activity            | Dasgupta et al. [121] Connaughton et al. [122] Palomer et al. [123] Nakamura et al. [124] |
|                                 | SIRT1                    | FAO, Biogenesis         | Kitada et al. [146] |
|                                 | AMPK                     | Mitochondrial homeostasis| Herzig et al. [133] Seabright et al. [134] |
|                                 | CaMK-IV                  | ΔΨm, fission, fusion, autophagy | Zhang et al. [136] |
|                                 | UCP2                     | ΔΨm, ROS                | Mao et al. [129] Donadelli et al. [135] |
|                                 | RIPK3                    | Autophagy               | Zhou et al. [132] |
|                                 | NO, H₂S, ROS             | PDC activity, TCA cycle, ETC complexes | Brown et al. [125] Erika et al. [126] Murphy et al. [127] Zorov et al. [128] |
| Hormone                         | Thyroid hormones         | Biogenesis autophagy    | Yu et al. [141] Marín-García et al. [142] Yau et al. [143] |
|                                 | Insulin                  | OXPHOS                  | Szendroedi et al. [144] Tubbs et al. [145] |
mitochondrial DNA and n-formyl peptides (n-fp) [155], are released to the cytosol where they could be sensed by various PRRs to activate the immune response.

The specific regulatory effects of mitochondrial metabolism on the innate immune pathway are influenced by metabolites in the metabolic pathway. TCA is blocked by down-regulation of isocitrate dehydrogenase and overexpression of immune-responsive gene 1 protein (IRG1) [156, 157], resulting in the conversion of accumulated citrate to itaconate [158, 159]. Iタonate can highly activate macrophages [160, 161] but also inhibit complex II (also known as succinate dehydrogenase), which prevents succinate from being oxidized [160]. Furthermore, succinate oxidation governs the inflammatory phenotype of the macrophage, as indicated by increased inflammatory gene expression and decreased anti-inflammatory gene expression [162, 163].

Conclusion

OXPHOS is the metabolic pathway of most cells in the physiological state, but during sepsis, the metabolism of cells is reprogrammed to glycolysis. Cells use both mechanisms to enhance their defenses in adverse situations. Crosstalk between immune activity and metabolic reprogramming during sepsis shows that switching to glycolysis increases immune activation, but that excessive glycolysis paradoxically causes immunosuppression. As the most key factor affecting tissue tolerance during sepsis, glycolysis can transiently maintain cellular vital activity, prolong survival, protect organs from ATP deficiency-induced death in sepsis, and in some way reduce oxidative damage to mitochondria and cells by OXPHOS. But, for achieving recovery of cellular functional activity in organs, the well-timed restoration of OXPHOS is the most necessary process. Whereas the basis of repairing OXPHOS is to ensure that mitochondrial structure and function are maintained, mitochondrial protection deserves more attention in the treatment of sepsis.

However, facing metabolic differences among different cell types and different severity of the disease, the most important question we need to consider is how to find the best time to use these reprogramming mechanisms. The same metabolic modality may lead to opposite results, e.g. glycolysis is beneficial for immune cell activation but detrimental in TECs [164]. Early restoration of OXPHOS appears to be the best option, but OXPHOS is also harmful to the fragile mitochondria and cells during sepsis. The metabolic flexibility determines the efficient operation of the metabolic reprogramming, which favors cells’ ability to adapt to adverse conditions. The fixable metabolic patterns due to loss of metabolic flexibility exacerbate cell dysfunction. To take full advantage of the crosstalk between metabolic reprogramming and cell function, we also need to find the key regulators that modulate the metabolic flexibility of the cell. However, we presently don’t recognize enough about septic metabolism and will face significant challenges in the future. Mitochondria, as the core organelles of cellular metabolism, could be a breakthrough to exploit metabolic reprogramming.

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