Macrophage metabolism reprogramming in sepsis: Pathogenesis and therapeutic implications (Review)

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Abstract. Sepsis is a life-threatening syndrome of organ dysfunction caused by infection, characterized by complex pathogenesis and high clinical mortality. As innate immune cells, macrophages serve a pivotal role in the initiation, progression and resolution of sepsis. The present review focuses on the key molecular nodes and signaling pathways of macrophage metabolic reprogramming in the process of sepsis. Key mechanisms include: i) The mammalian target of rapamycin-hypoxia inducible factor-1α (HIF-1α)-pyruvate kinase M2 axis as the primary regulator of glycolytic flux and pro-inflammatory cytokine production; ii) tricarboxylic acid cycle interruption leading to succinate accumulation, which amplifies HIF-1a signaling and promotes interleukin-1β release via G protein-coupled receptor 91, thereby exacerbating inflammation; iii) triggering receptor expressed on myeloid cells 2-SH2-containing protein tyrosine phosphatase-1 axis-mediated impairment of fatty acid oxidation, promoting lipid accumulation and pro-inflammatory activation; and iv) amino acid depletion contributing to immune paralysis. In view of the 31.5% global mortality (21.4 million mortalities in 2021) caused by sepsis, a shift from supportive treatment to precise immune metabolism intervention is needed. The present article uniquely integrates the coordinated regulation of glucose, lipid and amino acid metabolic networks of macrophages in sepsis, and expounds the research status of immune metabolism in sepsis, in order to provide reference for the clinical treatment of sepsis. Targeted modulation of macrophage metabolism offers a new direction for individualized immunometabolic therapy in sepsis.

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Contents

1. Introduction

Sepsis represents a form of systemic inflammatory response syndrome triggered by severe infections characterized by systemic dissemination disease and capable of causing multi-organ impairment. It accounts for a substantial global burden of morbidity and mortality (1), contributing to 20-40% of in-hospital mortalities (2,3). The Global Burden of Diseases, Injuries and Risk Factors Study 2021 showed that there were ~166 million sepsis cases in the world in 2021, resulting in 21.4 million sepsis related mortalities. This notable figure accounts for 31.5% of the total mortalities in the world, indicating that nearly one third of human mortality is due to sepsis (1,4). The epidemiological situation is also not optimistic. Although the number of sepsis related mortalities due to infection decreased before 2019, a sharp increase was observed between 2020 and 2021. This is mainly caused by the coronavirus disease 2019 pandemic (5). In addition, sepsis is increasingly considered as a fatal complication of non-communicable diseases. In 2021, stroke, chronic obstructive pulmonary disease and cirrhosis led

to 5.81 million sepsis related mortalities (4). This demographic change, especially since 1990, has seen an increase of 230% in adult morbidity. Therefore, the innate immune response of the host to the inducement of infection and chronic metabolic dysfunction must also be taken into account (4). A hallmark of sepsis is profound immune dysregulation, leading to tissue damage, organ failure and ultimately mortality, distinguishing it from uncomplicated infections (6,7). Excessive cytokine release, commonly termed a 'cytokine storm', can exacerbate tissue damage and promote systemic inflammatory response syndrome (SIRS) (8). Notably, sepsis involves the concurrent occurrence of hyperinflammation and immune suppression (2), which can lead to mortality either during the acute inflammatory phase, frequently associated with multiple organ dysfunction syndrome (MODS), or through progression to protracted inflammation, immune paralysis and organ failure (9).

Macrophages are central to immune homeostasis and inflammation regulation, notably influencing the onset and progression of sepsis (10). They exhibit remarkable heterogeneity and plasticity, polarizing into classically activated (M1, pro-inflammatory) or alternatively activated (M2, anti-inflammatory) states in response to environmental cues (11). During sepsis, macrophage metabolism, primarily involving glucose, lipid and amino acid pathways, deviates markedly from its physiological state. This metabolic reprogramming critically regulates immune function, supplying cells with the nutrients and energy required to adapt to environmental stresses and immune challenges (12).

The present review aims to reframe the understanding of macrophage metabolism in sepsis. We hypothesize that metabolic reprogramming is not merely a passive consequence of activation but an active driver of macrophage function. While previous studies have extensively cataloged individual metabolic pathways, such as the Warburg effect or the kynurenine pathway in isolation, the present review distinguishes them by proposing an integrated model (13-15). How glucose, lipid, and amino acid fluxes are hierarchically synchronized by specific metabolic checkpoints is delineated. Furthermore, the present review uniquely bridges basic signaling hubs with clinical biomarkers, providing a stage-specific therapeutic roadmap that addresses the dynamic nature of sepsis. It should be noted that although the M1/M2 classification provides a basic conceptual baseline, it is increasingly recognized that macrophage activation in sepsis is a multidimensional and dynamic process, rather than two discrete states. The present review, while using these terms for clarification, also acknowledges that the sepsis microenvironment determines a complex activation environment. Targeting immunometabolic crosstalk in macrophages is key to developing more effective and personalized sepsis therapies.

2. Search strategy and selection criteria

In order to ensure a comprehensive and up-to-date analysis of macrophage metabolic reprogramming in sepsis, a systematic survey of relevant literature was performed. Articles published from its establishment to February 2026 were searched on websites such as PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com/), with a particular focus on high-impact research from the past 5 to 10 years. The search strategy employed Boolean logic with specific term combinations, such as ('sepsis' OR 'septic shock') AND ('macrophage') AND ('glycolysis' OR 'fatty acid oxidation' OR 'immunometabolism' OR 'metabolic reprogramming').

The selection of papers was based on the following inclusion criteria: i) Peer-reviewed English original research articles or comprehensive reviews; ii) studies of the molecular mechanism of metabolic flux of macrophages in sepsis; or iii) clinical trials or observational studies evaluating metabolic biomarkers and therapeutic interventions for sepsis. Exclusion criteria included: i) Conference abstracts or preprints that are not peer-reviewed; ii) research focusing only on non-infectious inflammatory conditions; or iii) reports with insufficient experimental details or unreliable methods.

3. Phenotype transition of macrophages in sepsis

In the early stage of sepsis, which is the hyper-acute phase, the encounter between pathogen associated molecular patterns (PAMPs) and toll-like receptors (TLRs), such as TLR4, triggers a robust pro-inflammatory cascade. This 'cytokine storm' is characterized by the dominance of cells exhibiting M1-like features, driven by the nuclear factor κ-B (NF-κB) pathway and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB or Akt)/mammalian target of rapamycin (mTOR) axis. While this phase is essential for initial pathogen sequestration, persistent hyper-inflammation often precipitates SIRS and acute organ dysfunction (3,8,10,16).

As sepsis progresses, the host environment will transition to the stage of immune suppression or regression. Under the influence of anti-inflammatory mediators such as interleukin-10 (IL-10) and IL-4, macrophages undergo a compensatory shift toward M2-like states via the Janus Kinase/signal transducer and activator of transcription 6 (STAT6) and peroxisome proliferator activated receptor γ (PPARγ) pathways. While this transition is nominally reparative, the sustained presence of these cells often leads to immune paralysis, characterized by defective antigen presentation and impaired phagocytic capacity, thereby increasing susceptibility to secondary opportunistic infections (10,17,18).

However, the plasticity of macrophage function during sepsis represented by M1/M2 is overly simplified. A previous study has found that the existence of an atypical pro-inflammatory M2 ($M2_{INF}$) phenotype, indicating that glycolysis presents an $M2_{INF}$ pro-inflammatory phenotype, while inhibition of glycolysis weakens the $M2_{INF}$ phenotype (19). The coexistence of inflammatory and inhibitory markers within the same cell population is also a characteristic of clinical progression in sepsis. For example, the mTOR-hypoxia inducible factor-1α (HIF-1α) axis is not only a hub for M1 phenotype transfer, but also a core driver of enhanced glycolysis (Warburg effect). At the same time, the adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) pathway can regulate fatty acid oxidation (FAO) by inhibiting mTOR activity, thereby supporting the transition to the M2 phenotype. The conversion of pathways affects the phenotypic transfer of macrophages in sepsis, directly guiding their immune function and metabolic remodeling and determining the host's

defense strategies against infection, clinical manifestations and prognosis (13,20,21).

In recent years, the advent of single-cell RNA sequencing (scRNA-seq) has fundamentally reshaped the understanding of macrophage individual development and activation, with macrophage activation in sepsis now viewed as a multidimensional continuum rather than a discrete state. A prominent example is the discovery of lipid associated macrophages (LAMs), characterized by triggering receptor expressed on myeloid cells 2 (TREM2)-dependent transcriptional features. In sepsis, these LAMs coordinate lipid uptake and energy homeostasis. However, their excessive activation can damage FAO through the SHP1/Bruton's tyrosine kinase (BTK) axis, exacerbating the transition to immune paralysis (22-25). Network analysis also suggests that individual macrophages can simultaneously express markers of pro-inflammatory and anti-inflammatory programs, a phenomenon known as the 'mixed' or 'intermediate' phenotype (26,27). With the development of scRNA-seq, more subtypes of macrophages will be discovered in sepsis, allowing for targeted regulation of specific macrophage populations based on the real-time immune status of the patient (28-30).

4. Glycometabolism of macrophages in sepsis

Glucose metabolism is the foremost and most extensively studied metabolic pathway disrupted in septic macrophages. Under physiological conditions, macrophages utilize oxidative phosphorylation (OXPHOS), supported by a complete tricarboxylic acid (TCA) cycle and electron transport chain (ETC), to provide stable energy for M2 polarization and tissue repair (14,31). During early sepsis, PAMPs activate macrophages, inducing the Warburg effect where inflammation drives a shift from mitochondrial respiration to aerobic glycolysis (32-34). In the present review, alterations in glycolysis, the TCA cycle and the pentose phosphate pathway (PPP) are integrated within the context of sepsis progression (Fig. 1).

Glycolytic pathway. In early sepsis, M1 macrophages primarily rely on glycolysis, exhibiting enhanced glycolytic flux and diminished oxygen consumption (31,35), which disrupts the TCA cycle. This reprogramming enables rapid generation of energy and metabolic intermediates necessary for macrophage activity and function during infection (36). Upregulation of glycolytic enzymes, including pyruvate kinase M2 (PKM2), glucose transporter 1 (GLUT1), hexokinase (HK), phosphofructokinase-1 and 6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3), along with increased lactate production, further amplifies glycolytic activity and promotes M1 polarization (37,38).

Mechanistically, the metabolic-transcriptional interface in septic macrophages is orchestrated by the functional transformation of PKM2 and its synergy with HIF-1a (39,40). Under inflammatory cues, PKM2 undergoes post-translational modifications, specifically phosphorylation and acetylation, triggering its transition to a dimeric form that translocates to the nucleus (39,41). Elevated serum PKM2 levels have been shown to be strongly associated with disease severity and organ damage (42). Once in the nucleus, PKM2 acts as a co-activator for HIF-1a to directly promote the transcription of pro-inflammatory genes and essential glycolytic enzymes (16,43). Notably, this axis is further stabilized by the accumulation of succinate resulting from TCA cycle disruption at the succinate dehydrogenase (SDH) site (15,44). Intracellular succinate prevents HIF-1α degradation by inhibiting prolyl hydroxylases, thereby driving IL-1β production (45,46). Furthermore, extracellular succinate functions as a signaling molecule via G protein-coupled receptor 91 (GPR91) to sustain the pro-inflammatory M1 phenotype (47). Together, the PKM2-HIF-1α-succinate axis represents a metabolic checkpoint that bridges mitochondrial dysfunction with persistent glycolytic reprogramming.

HIF-1α upregulates glycolytic enzyme genes [such as HK2, PFKFB3 and lactate dehydrogenase (LDH)] and promotes GLUT1 synthesis. Moreover, it inhibits pyruvate entry into mitochondria and enhances its conversion to lactate by increasing LDH expression, thereby fueling glycolysis (48-50). Glycolysis, in turn, enhances HIF-1α translation and stability while promoting GLUT1 expression, creating a self-reinforcing loop that sustains glycolytic reprogramming (16,43). In the cytoplasm, dimeric PKM2 interacts with molecules such as high mobility group box-1 (HMGB1), enhancing transcription of glycolytic enzymes (GLUT1, LDH and HK) and skewing immune cells toward glycolysis, thereby amplifying the inflammatory response of M1 macrophages (40,41,51). These changes promote the release of late-phase pro-inflammatory mediators such as HMGB1 from macrophages (52). Extracellular lactate is taken up primarily via monocarboxylate transporters, facilitating HMGB1 lactylation through a p300 and CREB-binding protein-dependent mechanism.

Lactate can also be recruited to the nucleus via GPR81 to stimulate HMGB1 acetylation. Lactylated/acetylated HMGB1 is released via exosomes, increasing endothelial permeability and accelerating the progression of polymicrobial sepsis (53). HMGB1, a nuclear protein released extracellularly, exacerbates immune responses through TLR stimulation, direct cytotoxicity and platelet activation, contributing to disseminated intravascular coagulation and functioning as a damage-associated molecular pattern (54). Early clinical studies demonstrated elevated HMGB1 levels in sepsis, positively associating with disease severity and mortality (55,56). A previous study of 218 critically ill patients (145 with sepsis, 73 without) also reported a positive correlation between blood HMGB1 and lactate levels ($r=0.144$; $P=0.035$), supporting the interplay between HMGB1 and lactate during sepsis (57). The clinical correlation observed between PKM2, lactate and HMGB1 levels forms a metabolic inflammatory feedback loop in the pathogenesis of sepsis. The elevation of these markers is not only a result of tissue damage, but also an indicator of the enhanced glycolytic state before organ dysfunction. This indicates that the therapeutic window for glycolytic inhibitors or PKM2 modulators must be strictly aligned with the initial surge of these circulating biomarkers, as their peak likely represents a point of no return for HMGB1-driven vascular failure.

Beyond signaling pathways, macrophages in sepsis-induced acute lung injury (ALI) often overexpress the Sprouty RTK signaling antagonist 4 (Spry4) gene. Notably, Spry4 deficiency has been shown to alleviate lung injury by activating the calcium/calmodulin dependent protein kinase kinase 2

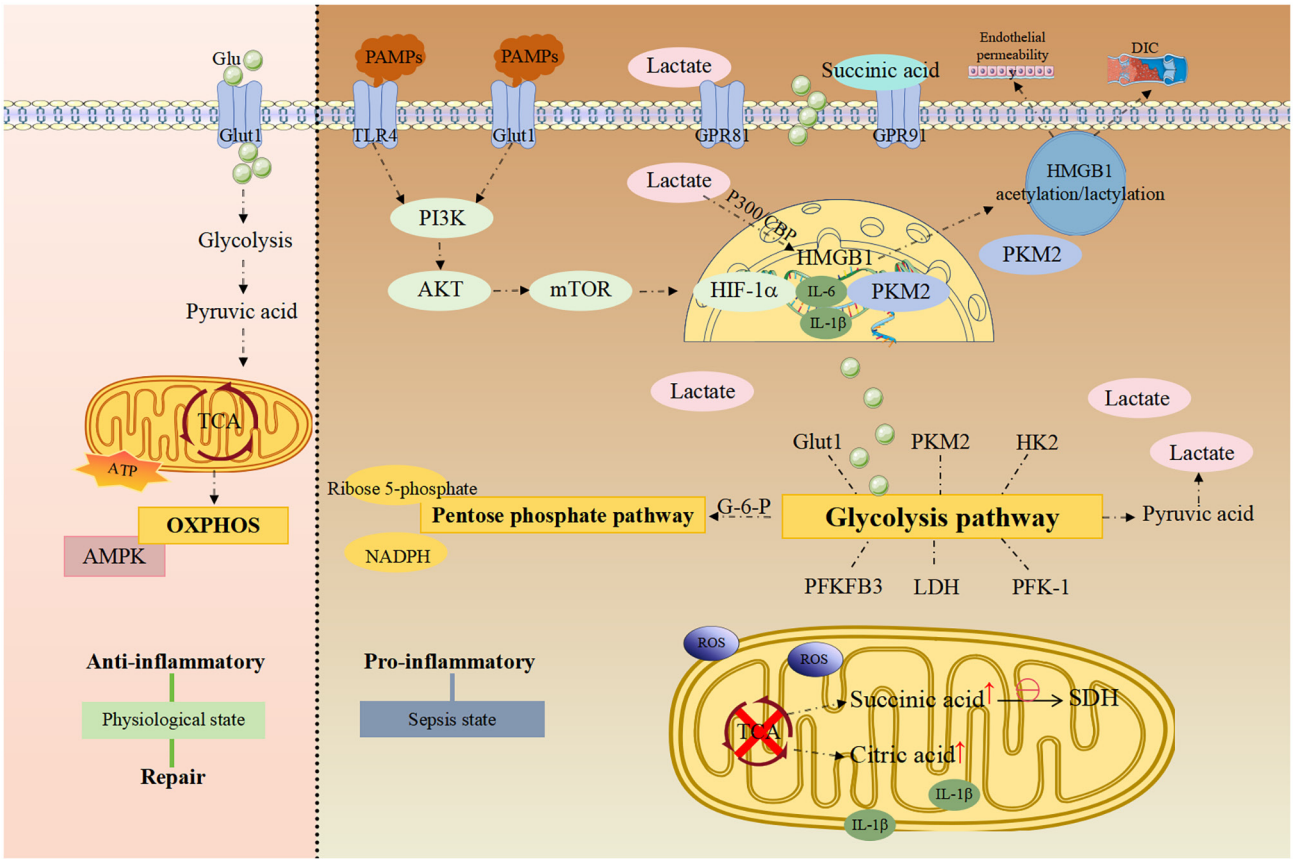

Figure 1. Comparison of macrophage glucose metabolism reprogramming under physiological and sepsis states. Under physiological conditions (left), the AMPK pathway in macrophages is phosphorylated and activated. Macrophages use OXPHOS as their core metabolic mode, relying on the complete TCA cycle and ETC to provide stable energy supply to support the anti-inflammatory/reparative phenotype of M2 macrophages. In sepsis (right), PAMPs (such as LPS) activate the AMPK-mTOR-HIF-1α-PKM2 axis and inhibits AMPK through TLR4 or GLUT1, driving the expression of key glycolytic enzymes (PKM2, GLUT1, HK2, PFKFB3, LDH, PFK-1), leading to an increase in the conversion of pyruvate to lactate. The G-6-P produced during glycolysis also increases the activity of the PPP pathway. Lactic acid produced through glycolysis pathway or recovered through GPPR81 promotes HMGB1 acetylation/acetylation through p300/CBP dependent mechanism, which is released in the form of exosomes, exacerbating endothelial damage and DIC. The dimeric form of PKM2 can interact with HMGB1 to promote glycolytic transcription. In addition, succinic acid accumulation caused by TCA cycle interruption can also be taken up by GPR91 cells, further increasing inflammatory factors and inhibiting SDH. The glycolysis pathway and intermediates of the TCA cycle, such as citrate and succinate, can serve as important metabolic branching points for lipid synthesis and epigenetic signaling. AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; OXPHOS, oxidative phosphorylation; TCA cycle, tricarboxylic acid cycle; PPP, pentose phosphate pathway; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; PAMPs, pathogen-associated molecular patterns; LPS, lipopolysaccharide; HIF-1α, hypoxia inducible factor-1α; PI3K, phosphatidylinositol 3-kinase; AKT, also known as protein kinase B or PKB; mTOR, mammalian target of rapamycin; TLR4, toll-like receptor 4; GLUT1, glucose transporter 1; PKM2, pyruvate kinase M2; HK2, hexokinase 2; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; LDH, lactate dehydrogenase; ROS, reactive oxygen species; G-6-P, glucose-6-phosphate; HMGB1, high mobility group box-1; P300/CBP, p300 and CREB-binding protein; GPR81, G protein-coupled receptor 81; DIC, disseminated intravascular coagulation; GPR91, G protein-coupled receptor 91; IL-1β, interleukin-1β; SDH, succinate dehydrogenase; PFK-1, phosphofructokinase-1.

pathway, contrasting with reports that Spry4 can aggravate sepsis progression (58). Another key metabolic regulator in sepsis is the PI3K/Akt/mTOR pathway, which also contributes to ALI pathogenesis (59). PI3K activation leads to downstream Akt activation, enhancing GLUT1 expression and glucose uptake. Activated Akt further increases HIF-1α expression via mTOR, explaining the preference for glycolysis even under aerobic conditions (60). In addition, the PI3K/Akt/mTOR axis overactivation not only prioritizes glycolytic flux, but also governs the intracellular availability of essential amino acids such as glutamine (Gln) and arginine, effectively linking glucose consumption to the protein synthesis machinery required for cytokine production. Taken together, these findings underscore the glycolysis-driven metabolic reprogramming in macrophages mediated by AMPK inhibition, PI3K/Akt/mTOR activation and PKM2 functional transformation, which promotes M1 polarization and inflammatory mediator release, ultimately driving immunometabolic imbalance and multi-organ damage in sepsis.

TCA cycle. Under physiological conditions, the TCA cycle maintains a balance between isocitrate dehydrogenase (IDH)-catalyzed conversion of isocitrate to α-ketoglutarate (α-KG) and SDH-catalyzed conversion of succinate to fumarate (14,31). In sepsis, the TCA cycle undergoes notable remodeling, characterized by two metabolic changes at the IDH and SDH sites (15,61).

In M1 macrophages, the activity of key TCA enzymes such as IDH and SDH is reduced, disrupting the mitochondrial oxidative respiration chain. This leads to partial TCA cycle blockade, enhanced glycolysis and accumulation of intermediates such as succinate and citrate (61). Cytosolic ATP-citrate

lyase cleaves accumulated citrate to provide acetyl-CoA for fatty acid synthesis, supporting production of inflammatory mediators such as prostaglandins and nitric oxide (NO) (62,63). Furthermore, excess citrate-derived acetyl-CoA affects epigenetic regulation by serving as a core donor for histone acetylation, which upregulates genes involved in inflammatory responses, such as IL-6 and IL-1β (64,65). Epigenetically, mitochondrial sirtuin 3 deficiency leads to hyperacetylation of TCA enzymes, increasing lactate and nicotinamide adenine dinucleotide production and contributing to sepsis-induced myocardial dysfunction (66).

Enhanced glycolysis and TCA disruption jointly increase lactate production. Lactate can serve as a precursor for histone lactylation [such as histone H3 lysine 18 lactylation (H3K18la], upregulating M2-related genes including arginase 1 (Arg1). This mechanism may serve a role in late-stage sepsis immunosuppression (67). M2 macrophages maintain an intact TCA cycle. Clinical data show elevated H3K18la levels in peripheral blood mononuclear cells from critically ill patients with sepsis, positively associating with Arg1 mRNA expression and disease severity (68). This suggests that early inflammatory responses driven by TCA interruption and its metabolites may lay the groundwork for later epigenetic reprogramming and phenotypic shifts. Other studies demonstrated that alveolar macrophages (AMs) in early ALI exhibit weak glycolytic capacity, predominantly displaying an M2 phenotype that relies on OXPHOS for cytokine production during lipopolysaccharide (LPS) activation (69). However, under extreme hypoxia, such as when ALI progresses to acute respiratory distress syndrome, HIF-1α activation promotes a shift in AMs to an M1 phenotype, transitioning from OXPHOS to glycolysis (70,71).

PPP. The PPP branches from glycolysis (at glucose-6-phosphate and fructose-6-phosphate) and serves two key roles in septic macrophages (13,72): Synthesis of ribose-5-phosphate and generation of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH).

Ribose-5-phosphate provides nucleotide precursors for macrophage proliferation (72). NADPH produced by glucose-6-phosphate dehydrogenase (G6PD; the rate-limiting enzyme of PPP) supports macrophage survival during infection. NADPH also maintains redox balance and fuels reactive oxygen species (ROS) production via NADPH oxidase to eliminate pathogens (13). Notably, M1 macrophages exploit both glycolysis and the PPP to meet their ATP demands (14,44). During sepsis, downregulation of carbohydrate kinase-like protein (CARKL/SHK), a factor co-localized with G6PD, increases PPP activity. CARKL/SHK is typically highly expressed in M2 macrophages (15,73). Inhibiting CARKL drives macrophages toward M1 polarization, enhancing ROS-mediated bacterial killing but also increasing the risk of tissue damage (13).

5. Lipid metabolism of macrophages in sepsis

Under physiological conditions, macrophages maintain lipid homeostasis through balanced FAO for energy and cholesterol efflux for membrane integrity (14,63,74,75). In sepsis, this balance is disrupted: Increased lipid uptake, impaired FAO and disturbed cholesterol metabolism collectively promote inflammation, lipotoxicity and organ damage (Fig. 2).

Fatty acid metabolism. During sepsis, macrophage lipid uptake capacity is enhanced, increasing fatty acid metabolic activity (76). This uptake depends largely on the expression of fatty acid transporters such as cluster of differentiation 36 and carnitine palmitoyltransferase 1a (CPT1a). Upregulation of these transporters facilitates efficient fatty acid acquisition (63,77). Additionally, mitochondrial STAT3 further promotes FAO by stabilizing CPT1a via ubiquitin specific peptidase 50-mediated deubiquitination (78), enhancing fatty acid entry into mitochondria. Lipid metabolites can also act as immune signaling molecules; for example, saturated fatty acids such as palmitic acid promote pro-inflammatory responses in macrophages via TLR signaling, increasing tumor necrosis factor-α (TNF-α) and IL-6 production (79,80). These pro-inflammatory cytokines, in turn, further enhance fatty acid uptake and activate metabolic regulators such as AMPK and mTOR (81,82). Although AMPK activation can promote autophagy and FAO to counteract inflammation (77,83), its activity is typically suppressed in sepsis.

In late-stage sepsis, macrophages rely mainly on mitochondrial OXPHOS and FAO for tissue repair (15,84). However, reliance on FAO often leads to imbalances. First, anti-inflammatory cytokines such as IL-4 and IL-10 may contribute to immune suppression (10). Second, rapid glycogen depletion causes transient hyperglycemia and increased triglyceride lipolysis, elevating free fatty acid (FFA) and glycerol levels and manifesting as impaired FAO in sepsis. Dysfunction of PPARα and the glucocorticoid receptor exacerbates metabolic imbalance, leading to ketone body and glucose deficiency and promoting inflammation (85-87).

Excessive lipid accumulation disrupts intracellular homeostasis and aggravates inflammation. However, not all lipid metabolites are detrimental. For instance, ketone bodies directly protect cells and negatively regulate inflammation by activating the β-hydroxybutyrate receptor GPR109A and inhibiting the NOD-like receptor domain-containing protein 3 inflammasome (88,89). Prostaglandin E2 (PGE2) inhibits TNF-α and IL-6 production, while lipoxin A4, derived from arachidonic acid, inhibits PGE2 signaling and promotes M2 macrophage polarization (90). Moreover, other fatty acid metabolites also suppress inflammatory responses. Unsaturated fatty acids promote tissue repair by activating anti-inflammatory pathways such as PPARγ (91). Omega-3 fatty acids attenuate sepsis-induced inflammation and oxidative stress by increasing notch receptor 3 expression via downregulation of micro-RNA (miR)-1-3p and blocking the Smad pathway, thereby mitigating intestinal epithelial injury (92). Nevertheless, persistent lipid metabolic dysregulation can sustain M1 polarization, perpetuating chronic inflammation and tissue damage (3,63,93,94).

Clinically, lipid metabolism is linked to sepsis prognosis. Elevated serum FFA levels are positively associated with disease severity and can exacerbate sepsis by activating specific inflammatory pathways, further contributing to MODS (95). Alterations in essential fatty acid metabolism may disrupt the balance between pro- and anti-inflammatory mediators (such as eicosanoids and cytokines), leading to

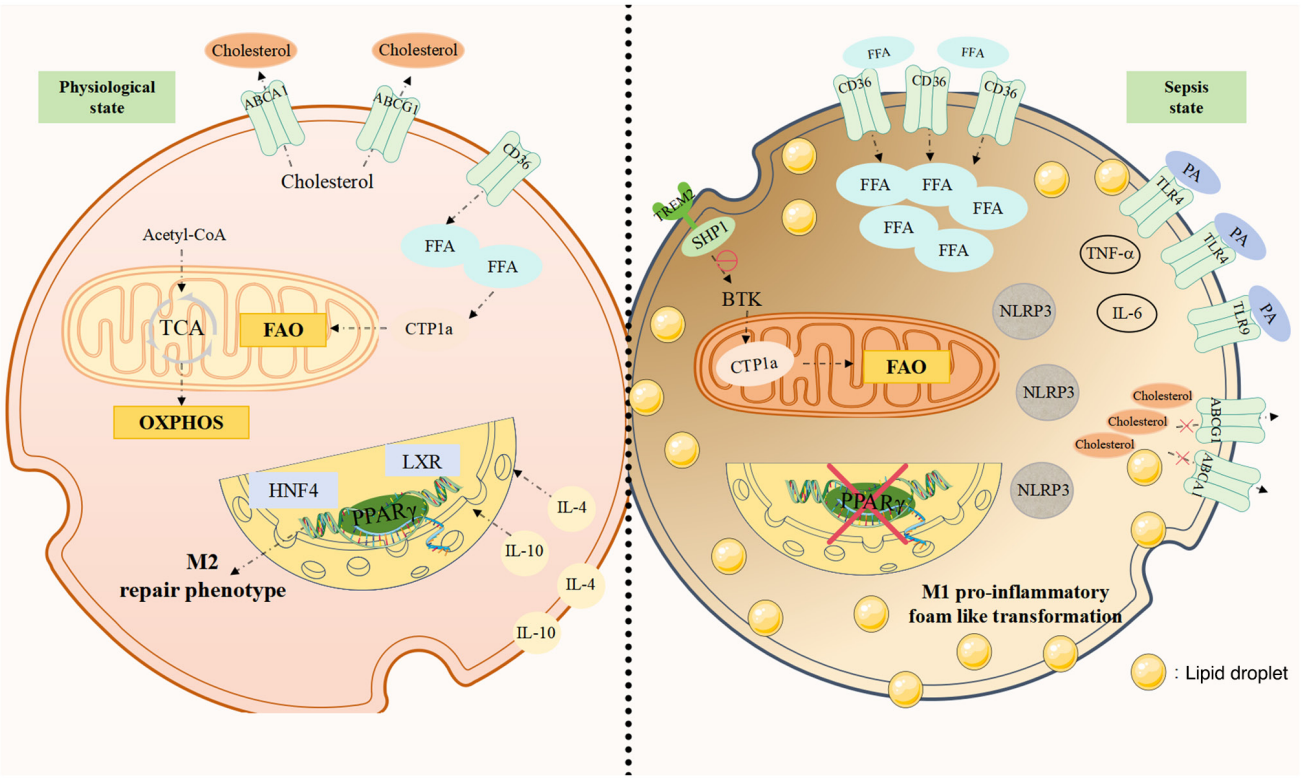

Figure 2. Comparison diagram of macrophage lipid metabolism reprogramming between physiological state and sepsis states. Under physiological conditions (left), macrophages maintain FAO dominated energy metabolism through CD36 and CPT1a mediated lipid uptake, while acetyl CoA enters the TCA cycle to support OXPHOS. ABCA1/ABCG1 mediates cholesterol efflux to stabilize cell membrane function. Anti-inflammatory factors promote M2 polarization through PPARγ signaling. In sepsis (right figure), lipid uptake (increased CD36) increases while FAO is impaired (especially inhibited by TREM2-SHP1 axis), leading to lipid accumulation and lipotoxicity. Cholesterol efflux disorder exacerbates lipid raft aggregation and TLR inflammatory signaling. In addition, saturated fatty acids and NLRP3 inflammasome activation drive M1 polarization dominant inflammation, while anti-inflammatory pathways such as PPARγ/LXR are inhibited. This lipid metabolic network is functionally coupled with glucose metabolism, where glycolytic-derived acetyl-CoA supports *de novo* lipogenesis, reflecting a high degree of substrate interdependency. FAO, fatty acid oxidation; CD36, cluster of differentiation 36; CPT1a, carnitine palmitoyltransferase 1a; TCA, tricarboxylic acid; OXPHOS, oxidative phosphorylation; ABCA1, ATP-binding cassette protein A1; ABCG1, ATP-binding cassette protein G1; IL, interleukin; PPARγ, peroxisome proliferator activated receptor γ; FFA, free fatty acids; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; NLRP3, NOD-like receptor domain-containing protein 3; LXR, liver X receptors; HNF4, hepatocyte nuclear factor 4; TREM2, triggering receptor expressed on myeloid cells 2; SHP1, SH2-containing protein tyrosine phosphatase-1.

immune dysregulation in sepsis (96). Additionally, elevated heart-type fatty acid-binding protein serves as a biomarker for early diagnosis and prognosis of sepsis-induced cardiomyopathy (97). These findings suggest that targeting lipid metabolic pathways may improve macrophage function and attenuate sepsis-induced inflammation. Therapeutically, mTOR inhibitors such as rapamycin promote FAO and autophagy to limit tissue damage and prevent excessive immune responses (98). Preclinical studies show that PPARα agonists improve survival in septic mice by restoring FAO and reducing lipotoxicity (87,99). Although this strategy awaits validation in human trials, it highlights the potential of PPAR activation in alleviating sepsis-related metabolic disorders (100).

Recent single-cell landscape studies have identified a specific subpopulation called LAMs, which differs from the classical M1/M2 classification system (22-24). The characteristic of LAM is the TREM2 dependent transcriptional program, which serves as a metabolic sensor to coordinate lipid uptake, lysosomal function and energy homeostasis. In sepsis, TREM2 serves a double-edged sword role in this subgroup. On the one hand, TREM2 signaling in LAMs helps prevent systemic lipotoxicity, promote the clearance of apoptotic cells and improve sepsis outcomes in liver and heart injury models (23,24). On the other hand, overactivation of TREM2$^+$ LAMs can lead to systemic hypercholesterolemia and increase susceptibility to sepsis by over-activating the SHP1/BTK axis, which in turn impairs FAO (22). Studies have found that knocking out TREM2 in macrophages reduces inflammation, organ damage, triglyceride accumulation and enhances FAO, improving survival in septic mouse models (25). This indicates that LAMs represent the metabolic adaptation of macrophages to the lipid-rich sepsis microenvironment, and its functional direction depends on the severity and stage of infection.

Cholesterol metabolism. Cholesterol, a sterol lipid, is a precursor for steroid hormones, bile acids and oxysterols (101,102), and also regulates various cellular functions while forming structural components of cell membranes along with cholesteryl esters (103). Both cholesterol and its lipoprotein carriers possess immunomodulatory properties, binding and neutralizing endotoxins to prevent PAMPs activation of TLRs (104).

During sepsis, serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) are markedly reduced (105,106), associating with increased mortality risk. Early clinical data

indicate that LDL-C levels are lowest at diagnosis, while HDL-C levels typically reach their nadir around the third day in hospital (107). However, previous studies suggest that while low levels of HDL-C may be a key contributor to mortality risk, reduced LDL-C concentrations may not be causative (106,108). A cohort study investigating the non-HDL-C/HDL-C ratio in patients with sepsis revealed a U-shaped relationship with 28-day mortality, both excessively high and low ratios were associated with increased mortality (109), highlighting the importance of monitoring this ratio. The U-shaped relationship between the comprehensive cholesterol ratio and mortality rate indicates that lipid homeostasis can serve as a buffering system. In addition to serving as energy precursors, lipoproteins also act as innate scavengers of pathogenic endotoxins. The precipitous drop in HDL-C observed in non-survivors reflects a critical failure in this protective capacity, positioning cholesterol profiles as functional indicators of the host's residual innate defense reserves rather than a simple metabolite. Animal studies demonstrate hypocholesterolemia during sepsis, with serum cholesterol levels inversely associated with inflammatory markers (110-112). Although well-documented, the mechanisms underlying hypocholesterolemia in sepsis remain unclear.

Cholesterol levels intricately influence macrophage signaling, particularly through lipid raft domains that modulate TLR4 and TLR9 signaling (113). Impaired cholesterol transport (such as due to ATP-binding cassette protein A1/ATP-binding cassette protein G1 defects) hinders efflux, leading to cellular cholesterol accumulation and lipid raft enlargement. This heightens macrophage sensitivity to TLR4 signaling and LPS, exacerbating inflammatory responses (113-117). Cholesterol metabolites also activate nuclear receptors such as hepatocyte nuclear factor 4a and liver X receptors. In infected macrophages, altered lipid metabolism can activate these receptors, modulating inflammatory mediator expression (118).

6. Amino acid metabolism of macrophages in sepsis

Amino acids serve not only as fundamental building blocks of cellular metabolism but also as key signaling molecules and regulators of immune cell functions, including those of macrophages (119). Sepsis primarily reprograms three key amino acid pathways in macrophages, aromatic amino acid, Gln and arginine metabolism, each prominent at different disease stages (inflammatory response and immune suppression) (Fig. 3).

Metabolism of aromatic amino acids. Aromatic amino acids tyrosine, tryptophan and phenylalanine, are among the most markedly altered metabolites in sepsis. A previous study noted marked increases in intermediates such as phenylpyruvate and L-phenylalanine, highlighting prominent dysregulation of aromatic amino acid metabolism in sepsis (120).

Tryptophan metabolism is particularly relevant to immune escape mechanisms in sepsis (121). Inflammatory cytokines such as interferon-γ induce indoleamine 2,3-dioxygenase gene transcription in macrophages, enhancing tryptophan degradation via the kynurenine pathway. Kynurenine and its derivatives suppress T-cell proliferation and modulate macrophage activity, promoting immunosuppression (121-123). Notably, kynurenic acid, a kynurenine pathway metabolite, facilitates the transition from M1 to M2 macrophages by inhibiting NF-κB signaling and alleviating septic colon injury (124).

The phenylalanine/tyrosine ratio also reflects immune activation status, and studies have identified phenylalanine and histidine metabolism as among the most markedly altered in sepsis (120,125). Excessive phenylalanine can inhibit protein synthesis and exert toxic effects on antibodies (120). A study of 63 patients with sepsis also found strong associations between phenylalanine metabolism and sepsis-associated acute kidney injury.

Gln metabolism. In macrophages, Gln is converted to glutamate by glutaminase and further metabolized to a-KG, which enters the TCA cycle for energy production (75). Gln metabolism-driven glutathione (GSH) synthesis provides energy and intermediates while helping maintain redox balance (13,14). Studies show a close association between Gln and M2 polarization; α-KG restores pyruvate dehydrogenase activity and supports M2 differentiation (13,14). Additionally, inflammatory mediator-stimulated metabolic reprogramming in macrophages depends on Gln. Macrophages can activate mTOR and other pathways to enhance Gln transporter expression, forming a positive feedback loop that amplifies immune responses (126,127). In sepsis-induced muscle atrophy, Gln therapy activates the mTOR pathway to alleviate muscle degradation (128). These cellular mechanisms indicate the potential of Gln in restoring metabolic balance and reducing organ damage in sepsis.

Substantial evidence suggests that Gln regulates cellular metabolism and function through post-translational modifications such as acetylation and succinylation, particularly in burn-induced sepsis (129,130). Gln also reduces oxidative stress by rescuing dysfunctional mitochondrial ETC complexes, protecting hepatocytes from inflammation-induced injury, a protective mechanism in burn sepsis (131). Moreover, Gln supplementation reduces sepsis-induced cardiomyocyte apoptosis in rat models (132,133). However, translating these beneficial mechanisms to clinical practice has yielded complex results. Some previous studies question the benefits of Gln in critically ill intensive care unit (ICU) patients and even associate its supplementation with development of chronic critical illness (134,135).

In the ICU, the benefit of Gln supplementation is highly dependent on timing, dose and host baseline status. Regarding timing, a study of 1,223 critically ill patients found that patients receiving Gln had a trend toward higher 28-day mortality compared with non-recipients (32.4 vs. 27.2%; adjusted odds ratio 1.28; 95% CI 1.00-1.64; P=0.05). In-hospital and 6-month mortality were also significantly higher in the Gln group (both P=0.02) (136). Dose-dependence was also significant, as evidenced by the significantly higher frequency of high urea levels in the glutamine group (13.4 vs. 4.0%; P<0.001). A large multicenter randomized trial indicated that high-dose parenteral Gln (>0.5 g/kg/day) should be avoided early in critical illness. This caution is mainly due to the metabolic substrate overload that occurs during the hyperacute phase of sepsis. In patients with multiple organ dysfunction, especially kidney and liver damage, the body's ability to handle nitrogen

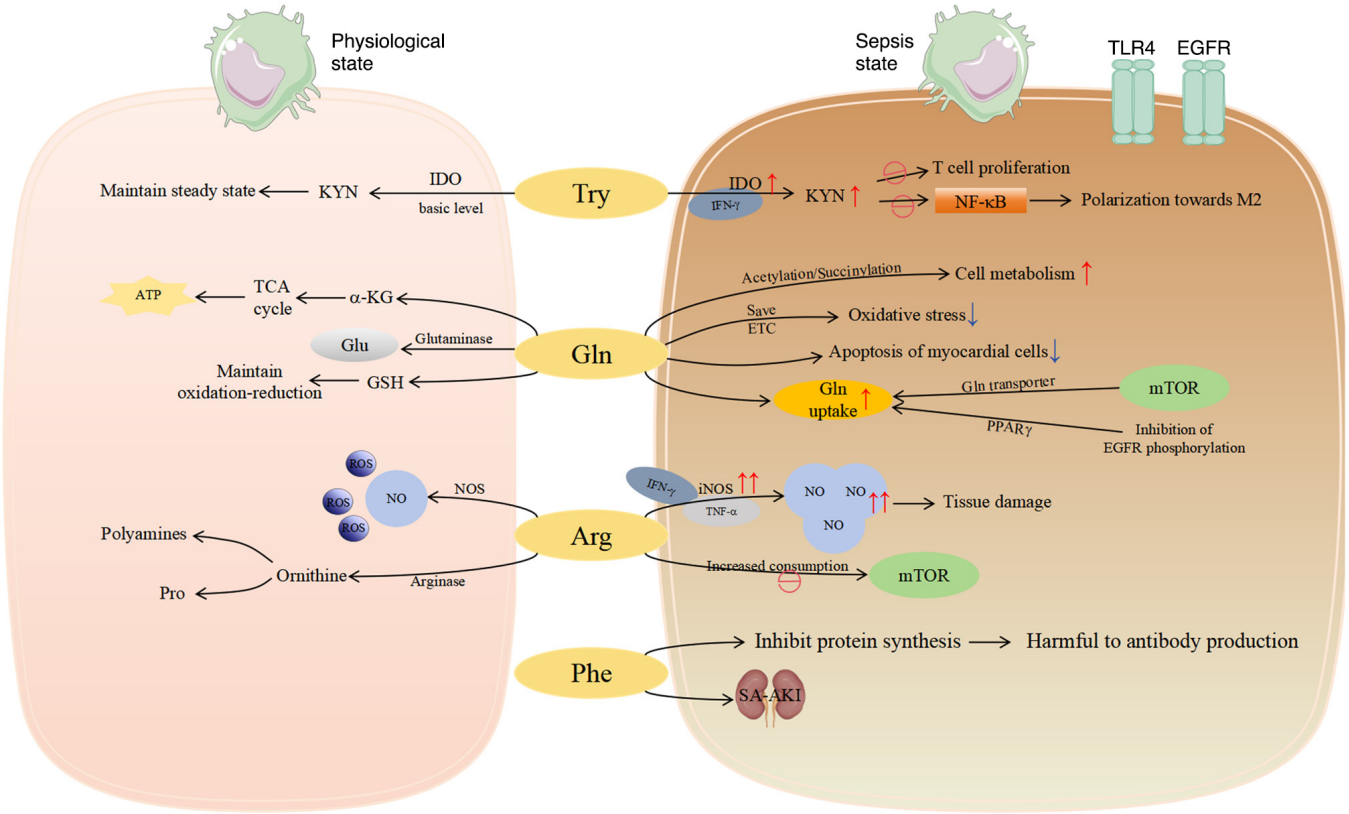

Figure 3. Comparison of amino acid metabolism reprogramming of macrophages under physiological and sepsis conditions. Under physiological conditions (left), amino acid metabolism maintains dynamic balance: Try regulates immune homeostasis by producing a small amount of KYN through low activity IDO. Gln maintains TCA cycle energy supply, produces Glu through glutaminase and supports antioxidant (GSH synthesis). Arginine produces appropriate amounts of NO (antibacterial) and ornithine (tissue repair) through the balance of NOS and Arg, respectively. In a sepsis state (right), amino acid metabolism is disrupted. IFN-γ induces high expression of IDO and accelerates the metabolism of Try along the KYN pathway. Phe metabolism is closely related to SA-AKI and can also cause toxicity to antibodies. The increase in Gln consumption enhances glycolysis and pro-inflammatory M1 polarization through mTOR activation. The TLR4/EGFR mTOR axis drives metabolic imbalance in sepsis, leading to M1 polarization dominance and the release of pro-inflammatory cytokines. Inhibition of EGFR can partially activate PPARγ to enhance Gln uptake and promote M2 repair. Overactivation of iNOS leads to depletion of arginine and excessive production of NO, and may inhibit the mTOR signaling pathway. When the glycolysis or lipid pathways are damaged, the metabolic flux of amino acids, especially the generated glutamine, can serve as an energy buffer to maintain mitochondrial integrity. Try, tryptophan; KYN, kynurenine; IDO, indoleamine 2,3-dioxygenase; Gln, glutamine; Glu, glutamate; GSH, glutathione; NO, nitric oxide; NOS, nitric oxide synthase; Arg, arginine; IFN-γ, interferon-γ; NF-κB, nuclear factor κB; Phe, phenylalanine; SA-AKI, sepsis associated-acute kidney injury; TLR4, toll-like receptor 4; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin; PPARγ, peroxisome proliferator activated receptor γ; iNOS, inducible nitric oxide synthase; ETC, electron transfer chain; ROS, reactive oxygen species; Pro, proline; TNF-α, tumor necrosis factor-α; a-KG, α-ketoglutaric acid; TCA, tricarboxylic acid.

load is markedly reduced. High doses of exogenous Gln can lead to excessive accumulation of metabolic byproducts such as ammonia and urea, which may exacerbate uremic toxicity or hepatic encephalopathy.

In addition, in the early stages of critical illness, the host may trigger large-scale catabolic reactions to mobilize endogenous amino acids. At this point, adding high doses of exogenous Gln may interfere with beneficial autophagy processes or inhibit the host's adaptive metabolic stress response, leading to increased mortality. The different results of large-scale Gln trials combine a fundamental clinical paradox, namely that the therapeutic benefits of amino acid supplementation depend on the metabolic stage of the patient rather than absolute dosage. The increase in mortality rate during the hyperacute phase indicates that exogenous nitrogen load may cause severe liver damage, while the same intervention during the recovery phase helps with redox balance and tissue repair. Therefore, a more cautious dosage of 0.3-0.5 g/kg/day should only be considered after the acute phase has subsided and organ function has stabilized (137). Regarding host status, patients with high metabolic demands (such as burns or trauma) may benefit from supplementation due to increased Gln consumption (elevating GSH and reducing oxidative stress). It may also benefit experimental neonatal endotoxemia and very low birth weight preterm infants. However, intracellular heat shock protein 70 deficiency due to Gln deprivation may increase post-sepsis mortality (138).

Ultimately, the clinical benefit of Gln is not absolute. Future research should move beyond the simplistic question of whether Gln is beneficial or harmful. Efforts should clarify these regulatory factors to identify sepsis subgroups most likely to benefit from Gln supplementation and develop individualized treatment strategies targeting related metabolic pathways, thereby improving sepsis outcomes.

Arginine metabolism. In macrophages, arginine is metabolized via two primary pathways: The nitric oxide synthase (NOS) pathway producing NO, and the arginase pathway producing ornithine. Regarding phenotype, NO can prevent

M1 macrophages from repolarizing to M2, while inducible NOS (iNOS) inhibition facilitates M1-to-M2 transition (139). By contrast, M2 macrophages metabolize arginine via Arg1, producing ornithine and urea.

In sepsis, macrophage iNOS expression increases in response to PAMPs (140). iNOS converts arginine to citrulline and NO. NO can react spontaneously with ROS to form reactive nitrogen and oxygen intermediates, serving as a key effector molecule in macrophage-mediated antibacterial and anti-inflammatory responses (31,140,141). However, excessive NO may also induce tissue damage (142). Additionally, arginine availability is often compromised in sepsis due to impaired *de novo* synthesis and accelerated catabolism, affecting arginine-dependent pathways such as mTOR signaling and thereby impacting macrophage function and survival (143,144). Arginine deficiency and reduced NO production are common in endotoxemia models and have been observed in ICU patients (145). Nonetheless, no consistent causal relationship has been established between low arginine levels and sepsis etiology (143), suggesting that arginine deficiency is not universal in all sepsis cases. Supplementing with arginine has been shown to reduce systemic inflammation and help maintain vascular homeostasis in sepsis (146,147). However, there is a complex paradox regarding the availability of arginine. Some researchers hypothesize that the reduction of arginine in host plasma during the acute phase of sepsis may be an adaptive defense mechanism to limit excessive NO production and subsequent oxidative stress substrates. On the contrary, long-term arginine deficiency can lead to immune dysfunction, such as impaired T cell proliferation and microcirculation (143,145,147). Therefore, the treatment goal should be to restore arginine to physiological levels, rather than reaching the level of an 'inflammatory cytokine storm' to support immune homeostasis (143,146,148).

Arginase activity is also altered during sepsis. Arg exists in two isoforms: Arg1 (cytosolic, liver-specific) and Arg2 (mitochondrial). Arg1 participates in the urea cycle, typically utilizing extracellular arginine to regulate its availability to neighboring cells (149). In M2 macrophages, Arg1 expression is promoted via the STAT6 pathway (150) and can be synergistically induced by IL-10 and LPS (151). In M2 macrophages, Arg1 expression is promoted via the STAT6 pathway and can be synergistically induced by IL-10 and LPS (152). Arg1 hydrolyzes arginine to ornithine and urea (153,154). Ornithine serves as a precursor for polyamine and proline synthesis; polyamines (such as putrescine and spermidine) participate in cell proliferation, while proline is crucial for collagen synthesis (155). Similar to Arg1, Arg2 expression is upregulated in human and mouse macrophages after LPS treatment (151). Arg2 downregulates succinate levels by promoting SDH (complex II) activity, further downregulating HIF-1α and IL-1 expression, promoting the M2 anti-inflammatory phenotype and enhancing mitochondrial respiration (156,157). However, in chronic inflammation models (such as atherosclerosis), Arg2 can also produce proinflammatory effects by increasing mitochondrial ROS. This suggests that it may have a similar dual role in sepsis, but further confirmation is needed (158). In summary, the balance between the NO and arginase pathways is disrupted; overactivation of iNOS consumes large amounts of arginine for NO production, affecting the arginase pathway and impairing normal macrophage functions such as phagocytosis and antigen presentation during the sepsis (159).

7. Targeting macrophage metabolism in sepsis therapy

Current sepsis management remains largely supportive, focusing on three main strategies: i) Early infection control; ii) fluid resuscitation and vasopressors; and iii) mechanical ventilation (160,161). Antimicrobial therapy is essential early in sepsis, typically involving broad-spectrum antibiotics to control infection and prevent progression (162). However, this approach carries a growing risk of antimicrobial resistance, estimated to contribute to 215,000 neonatal sepsis mortalities annually (163). Other source control measures (such as abscess drainage and debridement) and fluid resuscitation are also critical for correcting tissue hypoperfusion in septic patients (162). Nonetheless, these measures are often insufficient to improve prognosis for numerous patients (160).

Notable macrophage metabolic reprogramming occurs in sepsis, exacerbating inflammation while impairing immune regulation and tissue repair (164). Table I summarizes promising drugs/treatments, their mechanisms and key considerations based on this reprogramming (76,78,165-188). Although targeting macrophage metabolic pathways represents a strategic move toward precision immunomodulation, these interventions require a critical evaluation of their systemic trade-offs. For instance, while blocking the glycolysis-HIF-1α axis via 2-deoxy-d-glucose (2-DG) or PKM2 inhibitors effectively curbs the initial cytokine storm, such systemic inhibition often risks blunting the energy-intensive responses necessary for initial pathogen sequestration and clearance. Furthermore, the temporal application of mitochondrial restorers, such as itaconate or PPAR agonists, remains an evaluative challenge; promoting OXPHOS too early may lead to premature immunosuppression, whereas late administration may fail to rescue bioenergetically exhausted cells. Evaluating the metabolic changes and functional effects of macrophages must also consider disease tolerance, with the goal of maintaining organ function under pathogen load. The success of the aforementioned metabolic targeting strategies mainly depends on overcoming the current lack of macrophage specific delivery systems and inaccurate monitoring of real-time metabolic flux in patients.

8. Integrative analysis of translational challenges and metabolic interventions

A critical paradigm shift in immunometabolism is the recognition that metabolic reprogramming is not merely a collateral consequence of sepsis but a primary determinant of macrophage fate. We hypothesize that there can be a framework concept based on metabolic control in sepsis. In this framework, some nodes control the transition of sepsis stages. Central to the early hyper-inflammatory phase is the mTOR-HIF-1a-PKM2 axis, which facilitates the rapid glycolytic flux necessary for cytokine production. This pathway, while essential for initial pathogen clearance, concurrently primes the cell for late-stage exhaustion by generating specific metabolic signals. Figs. 1-3 depict the main metabolic changes in sepsis; however, these pathways

Table I. Therapeutic drugs and targets for sepsis based on metabolic reprogramming of macrophages.

Drugs/ treatments	Model/setting	Mechanisms	Net immunologic effect	Key safety considerations	(Refs.)
Metformin	Animal (septic mice/rats; sepsis-induced ALI/liver injury models); adult patients (≥18 years) within 48 h of meeting Sepsis-3 criteria, admitted to intensive care unit with oral or enteral access	Activates AMPK; inhibits HIF-1α-induced aerobic glycolysis; inhibits NF-κB; regulates the gut microbiota	Anti-inflammatory; attenuates lung/liver injury, reduces pyroptosis and apoptosis	In mice, 100 mg/kg does not cause kidney damage, and 200 mg/kg intraperitoneal injection has no notable toxicity; clinical dose translation pending	(165-168)
Resveratrol	Cells (LPS-stimulated macrophages); animal (septic mice)	Activates AMPK by Ca^{2+}/ CaMKKβ pathway	Enhances the phagocytic ability of macrophages; inhibits excessive inflammation; reverses endotoxin tolerance	Low dose may be more beneficial than clinical treatment, and specific concentrations need to be determined through preclinical experiments	(169,170)
2-DG	Animal (sepsis-induced AKI mice); cells (induced to inflammatory state by LPS)	Inhibits glycolysis; improves mitochondrial activity	Anti-inflammatory (alleviates oxidative stress); protects renal function; reduce cell apoptosis	Mice can take effect by drinking 0.4% water for 10 days and injecting 2 g/kg intraperitoneally	(171,172)
TRPV4	Cell (bone marrow-derived macrophages); animal (sepsis-induced ALI mice)	Enhances the uptake of GLUT1 glucose by macrophages through Ca^{2+} channel function and regulates stiffness-dependent glycolysis	Provides ATP for the maturation of lysosomes, promotes phagocytic function and alleviates ALI	No off-target effects in preclinical models; tissue-specific targeting needed	(173)
Ouabain	Cell (LPS-stimulated macrophages); animal (endotoxemic mice)	Inhibits LPS-induced upregulation of GLUT1 and HK2 at the transcriptional level; inhibits the upregulation of HIF-1α at the protein level	Anti-inflammatory (reduces pro-inflammatory cytokine production); attenuates endotoxemia; reduces liver and lung tissue damage	Narrow therapeutic window (high dose ouabain has potential cardiovascular toxicity)	(174)
Plumbagin	Cell (LPS-stimulated macrophages); animal (lethal endotoxemia/ sepsis mice)	Attenuates LPS-induced HMGB1 release in macrophages by inhibiting NOX4-mediated PKM2 expression	Anti-inflammatory (suppresses glycolysis-linked inflammation); protects against lethal sepsis	Cytotoxicity at high concentrations; lack of long-term toxicity data and human clinical trials	(175)
miR-210 knockdown	Cell (sepsis-associated macrophages); animal (sepsis/endotoxemia mice)	Inhibits glycolysis and M1 polarization	Anti-inflammatory (reduces 'cytokine storm'); mitigates organ damage	Delivery and specificity challenges of miRNA therapeutics *in vivo*	(176)

Table I. Continued.

Drugs/ treatments	Model/setting	Mechanisms	Net immunologic effect	Key safety considerations	(Refs.)
Targeting NLRC3	Cell (septic immuno-suppressive macrophages); animal (septic mice); human samples containing 35 patients in the immuno-suppressive stage of sepsis	Destroys NLRC3-mTOR-p300 complex; enhances the binding of NF-κB/NFAT5 to p300	Immune-modulatory (reverses glycolysis defects; restores immune function)	Unverified human safety of NLRC3 Unverified human safety of NLRC3	(177)
Targeting TIGAR	Cell (LPS-stimulated macrophages); animal (septic mice)	Inhibits TIGAR-TAK1 binding; blocks TRAF6-mediated TAK1 ubiquitination and autophosphorylation; suppresses NF-κB	Anti-inflammatory (alleviates systemic inflammation)	Lack of long-term toxicity data and human safety assessment; drug intervention may not be specific	(178)
Tamoxifen	Cell (sepsis-associated macrophages); animal (septic mice)	Promotes lipid metabolism; induces active caspase-1; enhances M1	Immune-modulatory (boosts pathogen clearance; balances inflammation)	The experimental concentration showed no macrophage toxicity; the combination of antifungal and antiviral drugs has no notable toxic side effects; long term use requires attention to known clinical risks	(179,180)
Tetracycline	Animal (septic mice; sepsis-induced lung injury models); cell (sepsis-associated macrophages)	Inhibits mitochondrial protein synthesis, increases FAO and improves lung injury repair	Inducing disease tolerance to alleviate organ damage	Lack of human clinical trial data; long term toxicity has not been evaluated; long term use may increase the risk of drug resistance	(76)
Curcumin	Cell (LPS-stimulated macrophages); animal (septic mice); peripheral blood mononuclear cells from patients with sepsis	Inhibits mitochondrial STAT3 and NF-κB activity	Anti-inflammatory (suppresses pro-inflammatory signaling); enhances tissue repair	Poor bioavailability; lack of mitochondrial STAT3 specific inhibitors makes it impossible to verify their direct toxicity and requires formulation optimization	(78)
AFRM	Cell (LPS-stimulated macrophages); animal (endotoxemic mice)	Adjusts the redox steady state; downregulates TLR4/NF-κB and MAPK/ERK	Anti-inflammatory (alleviates endotoxemia; suppresses pyroptosis)	Lack of long-term toxicity data and human trials; the particle size and biocompatibility of AFRM (0-200 μM) need further evaluation	(181)
IL-10	Cell (sepsis-associated macrophages); animal (septic mice)	Activates STAT3-signaling pathway; promotes M2 polarization	Anti-inflammatory (inhibits pro-inflammatory response; enhances tissue repair)	Excessive dosage/long-term use can lead to immune suppression and increased risk of secondary infection	(182,183)

Table I Continued.

Drugs/ treatments	Model/setting	Mechanisms	Net immunologic effect	Key safety considerations	(Refs.)
SLAMF7 upregulation	Cell (LPS-stimulated macrophages); animal (polymicrobial sepsis mice); human samples including 83 patients with sepsis	Synergistically inhibits TLR-MAPK/NF-κB-signaling pathway with SHIP-1; promotes M2 polarization	Anti-inflammatory (downregulates pro-inflammatory cytokines; reduces organ damage)	Lack of human clinical trials; the impact of long-term administration on immune homeostasis has not been evaluated	(184,185)
Macrophage-activating complexes (vitamin C lipid nanoparticles)	Cell (drug-resistant bacteria-infected macrophages); animal (drug-resistant bacterial sepsis mice)	Transmits mRNA of AMP-CatB	Pro-defense (enhances macrophage antibacterial activity), targets drug-resistant bacterial clearance; reduces resistance-related mortality	Lack of human clinical trial data; the risk of long-term *in vivo* accumulation of nanoparticles has not been evaluated	(186,187)
Biomimetic nanomodulator (mAOI NP)	Cell (SAE-related macrophages); animal (SAE mice)	Clears ROS, repairs mitochon drial damage, activates Nrf2/HO-1-signaling pathway; promotes M2 conversion	Anti-inflammatory (alleviates neuroinflammation); pro-resolution (improves SAE outcomes)	Lack of human clinical trial data; failure to assess long-term accumulation risk in the body	(188)

ALI, acute lung injury; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; HIF-1α, hypoxia inducible factor-1α; NF-κB, nuclear factor κ-B; LPS, lipopolysaccharide; CaMKKβ, calmodulin-dependent protein kinase kinase β; 2-DG, 2-Deoxy-D-glucose; AKI, acute kidney injury; TRPV4, transient receptor potential vanilloid 4; GLUT1, glucose transporter 1; ATP, adenosine triphosphate; HK2, hexokinase 2; HMGB1, high mobility group box-1; NOX4, nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase 4; PKM2, pyruvate kinase M2; miR/miRNA, microRNA; NLRC3, NLR family CARD domain containing 3; mTOR, mammalian target of rapamycin; NFAT5, nuclear factor of activated T cells 5; TIGAR, TP53 induced glycolysis regulatory phosphatase; TAK1, TGFβ-activated kinase 1; FAO, fatty acid oxidation; STAT3, signal transducer and activator of transcription 3; TLR4, toll-like receptor 4; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; AFRM, alanine fullerene redox modulator; IL-10, interleukin-10; SLAMF7, signaling lymphocytes activating molecule factor 7; TLR, toll-like receptor; SHIP-1, SH2-containing inositol phosphatase-1; AMP-CatB, antimicrobial peptide and cathepsin B; mAOI NP, macrophage membrane-coated antioxidant/anti-inflammatory nanoparticle; SAE, sepsis-associated encephalopathy; ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1.

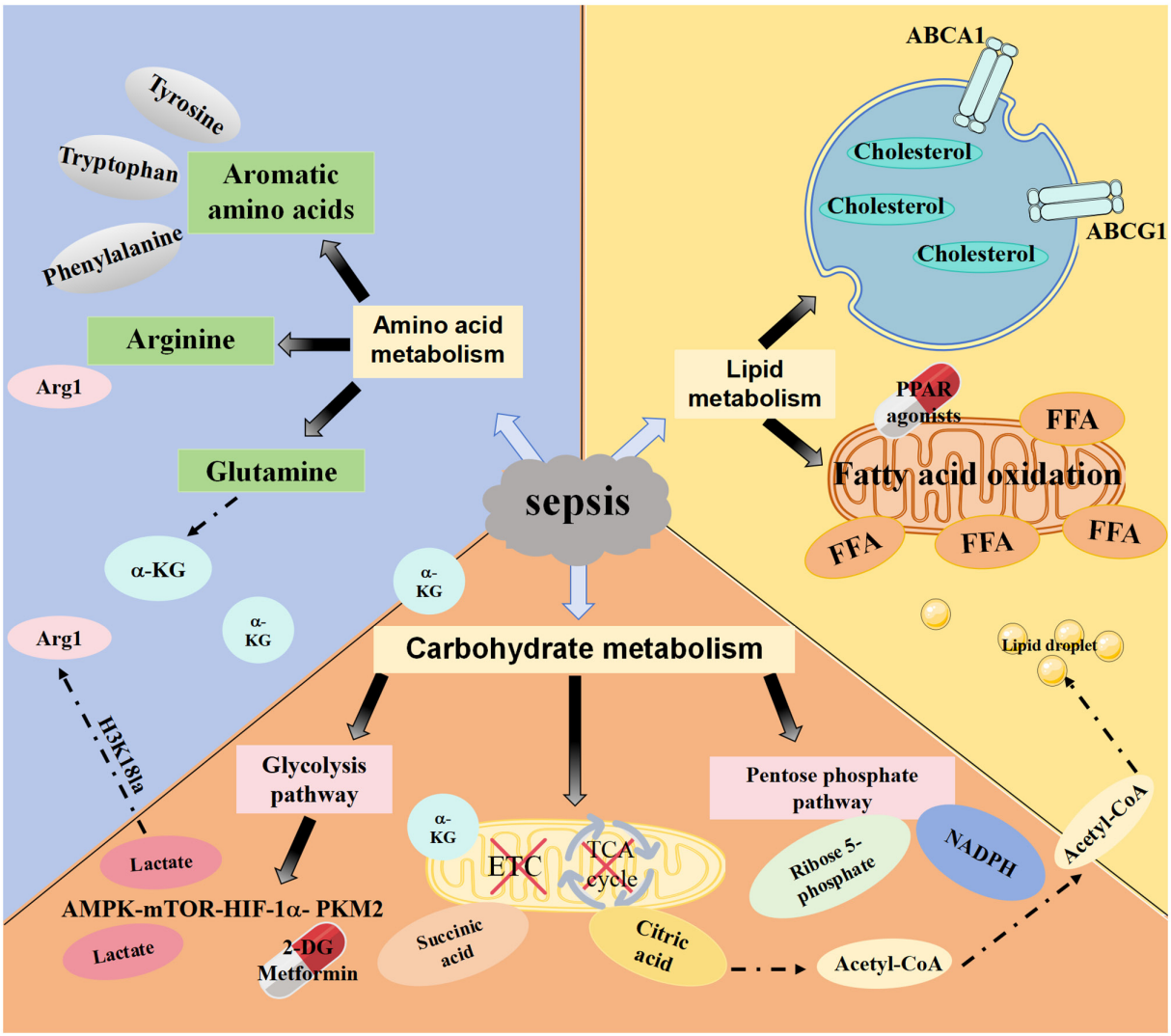

Figure 4. Comprehensive metabolism of macrophages in sepsis. The figure illustrates the non-linear interdependencies among carbohydrate, lipid and amino acid metabolism. Key regulatory nodes include the citrate-to-acetyl-CoA shunt for lipid accumulation, the glutamine-to-α-KG anaplerotic pathway for mitochondrial buffering and the lactate-H3K18la axis driving arginine metabolic shifts. Potential therapeutic agents (such as 2-DG, metformin and PPAR agonists) are mapped to specific metabolic checkpoints to provide a roadmap for precision immunometabolic therapy. Arg1, arginase 1; α-KG, α-ketoglutarate; H3K18la, histone H3 lysine 18 lactylation; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; mTOR, mammalian target of rapamycin; HIF-1α, hypoxia inducible factor-1α; PKM2, pyruvate kinase M2; ETC, electron transport chain; TCA, tricarboxylic acid; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; FFA, free fatty acid; PPAR, peroxisome proliferator activated receptor; ABCA1, ATP-binding cassette protein A1; ABCG1, ATP-binding cassette protein G1; 2-DG, 2-deoxy-d-glucose.

do not operate in parallel and isolation, but rather function as an interdependent regulatory network. In order to understand the non-linear characteristics of immune metabolism, the complex interactions between glucose, lipids and amino acids are depicted in Fig. 4. A single substrate is not linear, but is internally coupled through metabolic centers. For instance, the citrate accumulated from the truncated TCA cycle (Fig. 1) serves as the indispensable part of the *de novo* lipogenesis and lipid droplet formation observed in septic macrophages (Fig. 2). Simultaneously, the Gln-derived a-KG (Fig. 3) acts as a key energy buffer to sustain mitochondrial output when glycolytic flux is redirected toward lactate production. This metabolic interconnectedness implies that macrophage fate is determined by the global integration of these fluxes rather than isolated enzymatic changes.

We hypothesize that the lactate-H3K18la epigenetic axis, the TREM2-SHP1-BTK signaling pathway and itaconate-mediated mitochondrial modulation regulatory nodes in sepsis can function as synchronous elements rather than isolated metabolic changes (25,68,189,190). Specifically, the PKM2-HIF-1α-succinic acid circuit persists during the highly inflammatory phase, and accumulated lactate triggers the lactate H3K18la epigenetic axis. This histone modification controls macrophages in an immunosuppressive state by upregulating anti-inflammatory genes such as Arg1. Concurrently, the TREM2-SHP1-BTK axis serves as a critical regulatory node in response to systemic lipid dysregulation. Its overactivation inhibits mitochondrial FAO, leading to the bioenergetic failure observed in immunosuppressed macrophages (25). Additionally, the diversion of metabolic flux toward itaconate production regulates the TCA cycle by inhibiting SDH. In addition, the activation of nuclear factor erythroid 2-related factor 2 mediated antioxidant response limits oxidative damage and promotes the resolution of inflammation. These regulatory

nodes combine glycolysis, TCA cycle (via itaconate) and lipid sensors to form a theoretical framework for metabolic interventions targeting specific stages of sepsis. A unique contribution of the present review is linking the classification of therapeutic targets with stage specificity. As shown in Table I, drugs such as 2-DG or metformin have an early stabilizing effect by limiting the peak of pro-inflammatory glycolysis. And PPARα agonists or itaconic acid derivatives serve a late stage repair role to maintain mitochondrial homeostasis. Compared with the traditional methods, such as fluid resuscitation, broad-spectrum antibiotics and the static immunomodulatory strategies, this dynamic immune metabolism intervention may be beneficial for septic patient therapy.

As shown in Table I, successfully transferring these promising interventions from the laboratory to clinical treatment remains a challenging task. This conversion bottleneck is not due to a lack of mechanism depth, but rather to several interrelated barriers, starting with the profound heterogeneity of sepsis populations. The aforementioned molecules are not static markers, but dynamic regulatory factors whose biological effects depend on the pathological stage of sepsis and the organ microenvironment. For example, AMPK represents a key metabolic integration point. Although its inhibition is a hallmark of early pro-inflammatory glycolysis reprogramming, subsequent failure to reactivate can prevent the restoration of mitochondrial homeostasis and FAO. Therefore, therapeutic AMPK regulation requires precise timing to avoid damaging the initial host defense while preventing chronic metabolic failure. Similarly, TREM2 exhibits a notable dual effect in LAMs. Although it can alleviate systemic lipotoxicity and promote the clearance of apoptotic debris, this protective effect can also be offset by its potential to overactivate the SHP1/BTK axis, further leading to damage to FAO and exacerbating the transition to the immune paralysis stage.

Although Table I presents compelling experimental data, successfully translating macrophage metabolism-targeted therapies into clinical practice remains extremely challenging. This translational gap stems from several interrelated hurdles. First, heterogeneity of patients with sepsis, in genetic background, infection source and nutritional status, results in vastly different metabolic baselines and intervention responses (191). A treatment beneficial for one subgroup (such as acute inflammatory phase) may harm another (such as immunosuppressive phase). The context-dependent effect of Gln supplementation exemplifies this: It may benefit high-consumption states such as burns but show neutral or harmful effects in general ICU or renal insufficiency populations (134-136). Similarly, therapies validated in animal models, such as PPARα agonists, have demonstrated efficacy in restoring FAO and reducing lipotoxicity, yet their clinical application remains debated due to insufficient human data (87,99).

Second, intervention timing is crucial and must align with the dynamic metabolic phenotype of macrophages. Metabolic patterns shift markedly from early to late sepsis. Early sepsis is characterized by a glycolytic, pro-inflammatory M1 phenotype (Fig. 1), suggesting a therapeutic window for glycolytic inhibitors [such as 2-DG (171,172)] or PKM2 inhibitors. By contrast, advanced sepsis typically features immune suppression. At this stage, enhancing mitochondrial function [such as via PPARa agonists (87,99)] or carefully dosing IL-10 (182) may be more pertinent. Using glycolysis inhibitors during immunosuppression could further impair macrophage rescue capacity, underscoring the double-edged nature of targeting core metabolic pathways.

Third, the organ-specific context of macrophage niches necessitates tailored approaches. Metabolic reprogramming of alveolar macrophages in the lungs (Fig. 1) likely differs from that of Kupffer cells in the liver, potentially leading to divergent clinical manifestations even with the same pathogen. Systemically administered drugs may have varying effects on macrophages in different organs, offsetting overall therapeutic benefits. For instance, for biomimetic nanomodulators, such as macrophage membrane-coated antioxidant/anti-inflammatory nanoparticles (mAOI NPs), alleviating sepsis-associated encephalopathy may not necessarily ameliorate ALI or AKI (188).

Interventions targeting macrophage metabolism often aim to regulate organ function or improve long-term outcomes rather than prevent early mortality. Focusing on organ-specific endpoints, resolution of immunosuppression or metabolic biomarkers [such as circulating succinate, HMGB1 or lactate levels (42,44,57)] could provide more sensitive measures of drug efficacy in specific sepsis phases or patient subpopulations.

Despite the identification of key metabolic nodes, several critical limitations in current immunometabolism research must be acknowledged. Firstly, the majority of mechanistic insights are derived from LPS-induced or cecal ligation and puncture (CLP) rodent models. While CLP is considered the gold standard for polymicrobial sepsis, both models exhibit notable genomic and physiological discrepancies when compared with the clinical progression of human sepsis, particularly regarding the temporal dynamics of the inflammatory response (160). Therefore, direct clinical application requires careful verification. Secondly, the present review frequently generalizes 'macrophages' without fully distinguishing between tissue-resident macrophages (TRMs) and recruited monocyte-derived macrophages (MDMs). TRMs, such as alveolar macrophages and Kupffer cells, possess distinct ontogeny and metabolic baselines dictated by their organ-specific niches, whereas MDMs exhibit rapid, high-flux metabolic reprogramming upon recruitment to the infection site. The failure to account for this heterogeneity may lead to the misidentification of metabolic targets. Furthermore, macrophage metabolism does not function in isolation; it is markedly shaped by the inflammatory milieu provided by other cell types. Endothelial cells, neutrophils and lymphocytes influence macrophage metabolic states through the secretion of paracrine factors and competition for extracellular substrates such as glucose and Gln. Finally, metabolic centers that have been reported and studied were prioritized, as well as emerging therapeutic targets, which may naturally overlook less-characterized or niche signaling pathways that could also contribute to sepsis pathogenesis.

9. Conclusions and future perspectives

Macrophage metabolic reprogramming is a cornerstone of sepsis pathogenesis. It is an active driving process that shapes

the immune response from initial inflammatory outburst to eventual immune paralysis. The present review redefines sepsis as an interconnected pathological network in which glucose, lipid and amino acid metabolism disorders are interrelated, ultimately locking the host in a pathological state. Clinical biomarker data (such as serum PKM2 and HMGB1) was combined with basic signaling nodes such as the TREM2-SHP1 axis to propose a treatment framework arranged in chronological order, combining metabolic interventions with the dynamic stages of sepsis.

The therapeutic potential of targeting macrophage metabolism is immense yet complex. Multi-omics techniques (metabolomics and transcriptomics) should be used to define sepsis processes based on immunometabolic profiles. Tools for real-time patient metabolic monitoring need development. Finally, reliable metabolic biomarkers need to be identified to test targeted therapies in precisely defined patient populations at optimal timepoints during the disease course. Understanding and manipulating immunometabolism is not merely an adjunct to sepsis research but a fundamental framework for deciphering the complexity of the disease.

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Authors' contributions

TZ wrote, reviewed and edited the original draft. WZ wrote and reviewed the original draft. ZR reviewed the original draft. XF conceptualized and supervised the study and was involved with investigation and reviewing and editing the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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