

Immunometabolic Reprogramming in Experimental Sepsis: A Driver of Multiple Organ Dysfunction Syndrome

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Abstract: Sepsis is a life-threatening syndrome characterized by infection-induced systemic inflammation and immune dysregulation, commonly resulting in the development of multiple organ dysfunction syndrome (MODS), a leading cause of mortality in clinical practice. In decades, immunometabolic reprogramming has been identified as a critical mechanism that contributes to the progression of sepsis and the associated organ injuries. The review provides a systematic overview of the metabolic alterations in immune cells and organs in experimental models of sepsis. Key features include enhanced glycolysis, impaired mitochondrial function, and disturbed lipid metabolism, all of which are closely associated with organ damage. These metabolic adaptations influence immune responses and cell fate decisions, inter-organ crosstalk, and the development of MODS. A detailed examination is conducted on the temporal progression of pathological changes in established animal models, along with organ-specific metabolic dysfunctions and novel therapeutic targets. It emphasizes the importance of dynamic immunometabolic regulation, tissue-specific responses, and inter-organ interactions in the context of sepsis treatment. The integration of multi-omics technologies, identification of reliable biomarkers, and the development of personalized therapeutic strategies should be used to facilitate clinical translation of mechanistic insights.

Keywords: experimental sepsis, multiple organ dysfunction syndrome, immunometabolic reprogramming, inter-organ crosstalk, glycolysis

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Clinically, organ dysfunction is closely linked to increased in-hospital mortality.¹ Sepsis is also recognized as one of the leading causes of global mortality and critical illness.^{2,3} Although these definitions primarily address adult populations, the burden of sepsis in children is comparably severe. It remains a major cause of pediatric mortality worldwide, with significantly higher death rates observed in children who present with dysfunction in at least one non-primary organ system, including the respiratory, cardiovascular, coagulation, or neurological systems.⁴

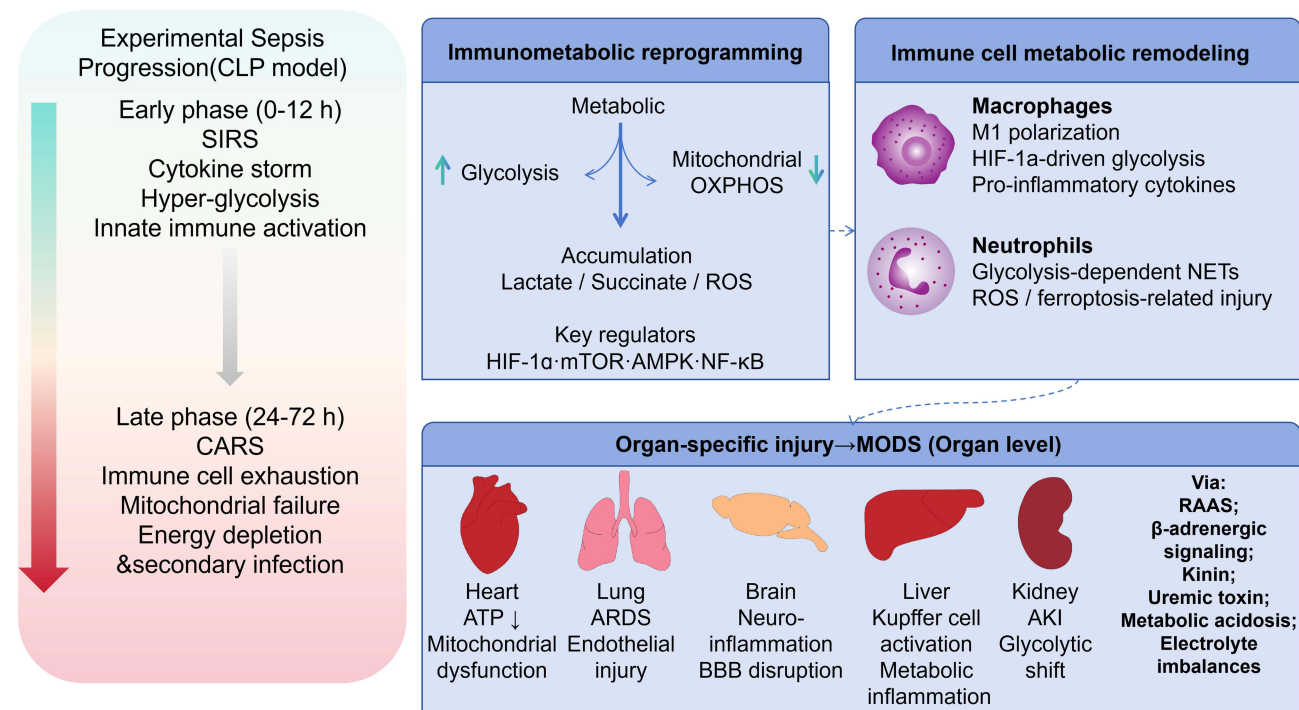
Multiple organ dysfunction syndrome (MODS) is a clinical condition defined by progressive and potentially reversible physiological impairment affecting two or more organ systems, typically initiated by acute insults such as sepsis.⁵ Organ dysfunction resulting from sepsis involves a complex network of inflammatory responses, including endothelial and microvascular impairment, immune and autonomic dysregulation, and alterations in cellular metabolism.⁶

Immunometabolism, as a central mechanism in sepsis, plays a critical role in promoting immune dysregulation during the septic response.⁷ A comprehensive understanding of immunometabolic alterations redefines the pathophysiological landscape of sepsis but also reveals how cellular energy dynamics influence immune function and contribute to organ damage, thereby identifying novel therapeutic targets.⁸ Given the current lack of effective treatments for the complex and life-threatening condition, such mechanistic insights are of urgent importance.

Both clinical and experimental evidence indicate that sepsis is not a single disease entity but a multifaceted syndrome involving interconnected immune dysregulation, microcirculatory impairment, metabolic disturbances, and progressive



Graphical Abstract



organ dysfunction. Animal models, by enabling control over experimental variables, serve as essential tools for delineating the causal relationships among these pathological processes. The review therefore focuses on experimental sepsis, with the aim of elucidating how immunometabolic reprogramming contributes to MODS under pathophysiological conditions and identifying potential targets for therapeutic intervention.

Experimental Animal Models of Sepsis

Animal models serve a fundamental function in sepsis research by offering a controlled platform to systematically investigate the metabolic reprogramming of immune cells under stress conditions. These models have significantly advanced the understanding of the complex interactions between immune function and cellular metabolism. In addition, animal models are essential translational tools for assessing the therapeutic potential of immunometabolic modulators in improving clinical outcomes in sepsis.

Given the closer resemblance to clinical presentation, the systemic models of sepsis were compared through the induction method, simulation characteristics, advantages and limitations of various models in Table 1. It is noteworthy that early sepsis models have been predominantly established in rodents, however, alternative animal species such as zebrafish are gaining attention for the utility in studying sepsis pathophysiology and therapeutic responses.⁹ Large animals, including pigs and dogs, share similar model induction approaches with rodents and offer advantages in evaluating organ function and immune responses with higher physiological fidelity. However, the use is limited by ethical considerations, high operational costs, and demanding maintenance requirements, making them more suitable for hypothesis-driven validation studies. The comparison among species was presented in Table 2. Notably, neonatal sepsis is a leading cause of mortality and disability in newborns, and the use of zebrafish larvae as a preclinical model holds great potential.¹⁰

Table 1 Experimental Model of Systemic Sepsis

Model	Induction Method	Simulation Characteristics	Advantages	Limitations	References
Cecal Ligation and Puncture (CLP)	Ligation of cecum followed by puncture causing fecal leakage	Polymicrobial infection and abdominal sepsis; simulates clinical polymicrobial infection; induces MODS; mimics dynamic process of human sepsis	Mimics dynamic immune responses; widely used	High variability due to inconsistent fecal leakage; high mortality rate	[11]
Lipopolysaccharide (LPS)	Injection of LPS	Simulates endotoxin mainly derived from Gram-negative bacterial infection in clinical sepsis; induces rapid systemic inflammatory response	Simple, highly controllable, reproducible; suitable for studying LPS-specific mechanisms	Some rodents show LPS insensitivity; not a true infection, only endotoxin exposure; lacks immunosuppressive phase	[12]
Bacterial Injection	Injection of bacteria such as <i>E. coli</i> , <i>vancomycin-resistant</i> <i>Enterococcus faecium</i> , <i>Staphylococcus aureus</i>	Simulates clinical monomicrobial infection; dose controllable; easy to operate; useful for studying specific pathogen-host interactions	Realistic infection process; adjustable severity; suitable for evaluating antimicrobial therapies	Usually an acute lethal model can not reflect complex immune dynamics	[13–16]
Peritoneal Contamination and Infection (PCI)	Intraperitoneal injection of fecal slurry	Simulates abdominal infection-induced sepsis; similar to clinical peritonitis or gastrointestinal perforation	Standardized modeling steps when using commercial fecal suspensions; minimal batch variation; no surgery required	Requires precise dosing; high doses induce sepsis but increase mortality; fluid resuscitation needed post-injection	[17]
Colon Ascendens Stent Peritonitis (CASP)	Insertion of stent into ascending colon causing continuous fecal leakage	Continuous peritoneal contamination; mimics clinical “leaky gut” type sepsis; induces more stable MODS	Avoids variability of fecal leakage seen in CLP; infection severity adjustable via stent diameter	More invasive and stressful to animals; higher cost and complexity	[18]
Two-Hit	Two consecutive insults, eg, LPS + CLP or trauma-hemorrhage + CLP	Mimics immunosuppression and secondary infection	More closely mimics clinical progression of severe sepsis	Experimentally complex; poor model reproducibility	[19,20]

Table 2 Comparison of Sepsis Models Across Different Species

Species	Cost	Operability	Similarity to Humans	Genetic Tools	Major Applications	References
Zebrafish	★★★★★	★★★★★	★★★	★★★	Innate immune mechanisms, live imaging, drug screening, neonatal validation	[9]
Mouse	★★★★	★★★★★	★★★	★★★★★	Mechanistic studies, immune response modeling	[11]
Rat	★★★	★★★★	★★★	★★	Organ dysfunction, cardiovascular and pharmacological studies	[21]
Rabbit/Sheep	★★	★★★	★★★★	★★	Moderate translational relevance, soft tissue or pneumonia-induced sepsis	[22,23]
Pig	★★	★★★	★★★★	★★	Translational research, therapeutic validation	[24]
Dog	★★	★★★	★★★★	★	Intensive care simulation, early clinical research	[25]
Non-human primate	★	★★	★★★★★	★	High-level translational and immunological validation	[26]

Note: Ratings are based on a five-star scale, from ★ (lowest/least) to ★★★★★ (highest/most).

Immunometabolic Reprogramming in Experimental Sepsis

Disease Progression of Experimental Sepsis

Over the past decades, the CLP model has been recognized as the representative experimental model to simulate systemic sepsis,²⁷ for replicating the entire progression from infection-induced systemic inflammatory response syndrome (SIRS) to late-stage immunosuppression known as compensatory anti-inflammatory response syndrome (CARS).²⁸ Its pathology encompasses cytokine storm, organ dysfunction, and metabolic imbalance,²⁹ inducing systemic manifestations similar to human MODS.^{30–32} The time-dependent characteristics of the model (as illustrated in Figure 1) make it ideal for studying immunometabolic reprogramming, the temporal relationship of organ injuries,³² as well as for evaluating related therapeutic interventions (Table 3).

Immune Cell Metabolism Orchestrates the Functional Transformation

In sepsis, immune cells undergo systemic metabolic reprogramming, known as immunometabolic reprogramming, in response to pathogenic stress, adapting to the highly dynamic inflammatory environment. A hallmark of the reprogramming is a shift from OXPHOS to aerobic glycolysis,⁴⁶ which is one of the most characteristic features of sepsis-related metabolic dysregulation and strongly associated with hyperinflammation and high mortality.⁴⁷ To mount an effective defense against pathogens, immune cells require rapid proliferation and biosynthesis of lipids and proteins. The processes are energy-demanding and often activated by pro-inflammatory signaling, resulting in enhanced glycolysis and anabolic pathways, alongside suppression of catabolic processes such as OXPHOS and fatty acid oxidation (FAO).⁴⁸

Immunometabolic reprogramming shapes immune cell phenotypes and contributes to inter-organ crosstalk disorders through the release of key metabolic intermediates such as lactate, succinate, and reactive oxygen species (ROS).^{49,50} These mediators further contribute to endothelial injuries,⁵¹ coagulation activation,⁵² and mitochondrial dysfunction,⁵³ all of which are central to

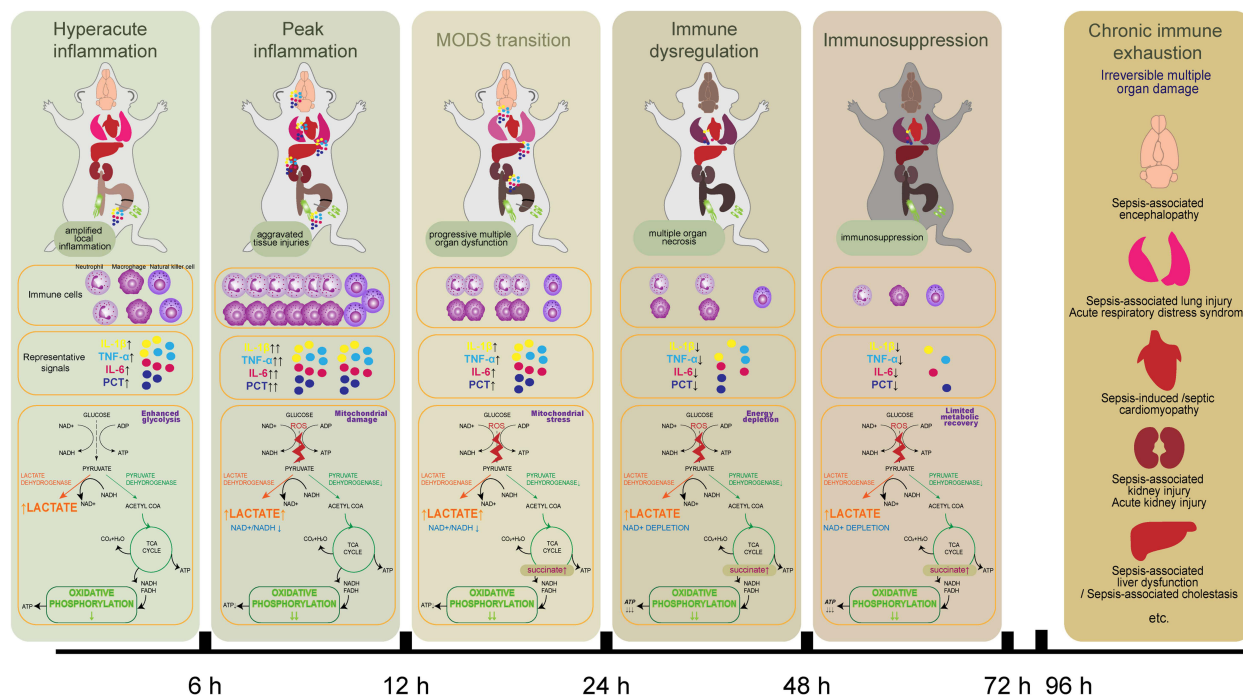


Figure 1 Temporal progression of immunometabolic reprogramming and organ dysfunction in CLP model. The temporal progression of immunometabolic alterations and corresponding pathological changes in CLP model was depicted at defined time points post-insult. The disease course progressed from hyperacute inflammation (0–6 h) and peak inflammation (6–12 h), through MODS transition (12–24 h) and immune dysregulation (24–48 h), to immunosuppression (48–72 h) and chronic immune exhaustion (>96 h). For each stage, key immune cell populations, representative cytokine profiles (eg, TNF- α , IL-6, IL-1 β , PCT), and shifts in metabolic pathways (enhancement of glycolysis with lactate accumulation, suppression of oxidative phosphorylation) were illustrated. Chronic immune exhaustion was indicated to be associated with irreversible multi-organ injury, including sepsis-associated encephalopathy, lung injury, respiratory distress syndrome, cardiomyopathy, kidney injury, liver dysfunction, and cholestasis. For the depiction of organs, a darker color indicated a greater degree of necrosis. During the MODS transition, the lung was shown in a lighter color due to pulmonary edema. Finally, in the immunosuppressive stage, mice were depicted in gray to represent a state of marked immune deficiency and a tendency toward increased mortality.

Table 3 Time-Dependent Disease Progression Characteristics of CLP Model

Time Point (Post-Operation)	Pathological Stage	Major Physiological/Pathological Events	Immune Status	Metabolic Characteristics	References
0-6 h	Hyperacute phase: inflammation initiation	Intestinal perforation and polymicrobial dissemination; amplified local inflammation; activation of systemic inflammatory signals	Strong inflammatory response with elevated delta neutrophil index and markers such as IL-1 β , TNF- α , IL-6, myeloperoxidase, and procalcitonin (PCT)	Enhanced glycolysis; increased lactate; suppressed oxidative phosphorylation (OXPHOS)	[33,34]
6-12 h	Peak inflammatory phase	Cytokine storm initiation in multiple organs causing aggravated tissue injuries; significant transcriptomic changes in organs	Persistent hyperinflammation; massive recruitment of neutrophils and macrophages	Increased oxidative stress; mitochondrial damage	[32,35,36]
12-24 h	MODS transition phase	Progressive multiple organ dysfunction (eg, increased alanine aminotransferase and blood urea nitrogen, pulmonary edema, renal tubular degeneration)	Signs of immune exhaustion appear: lymphocyte dysfunction, impaired macrophage and T cell activity	Dysregulated lipid metabolism; enhanced proteolysis; mitochondrial stress; succinate accumulation	[37–40]
24-48 h	Immune dysregulation phase	Local hemodynamic abnormalities; multiple organ necrosis	Lymphocyte apoptosis; T cell exhaustion; immunosuppression	High metabolic consumption with energy depletion; NAD ⁺ depletion; reduced OXPHOS capacity	[41–43]
48-72 h	Immuno-suppressive Phase	Marked immunosuppression; susceptibility to secondary infections; peak sepsis-related mortality	Reduced antigen presentation; decreased inflammatory cytokines; increased vulnerability to secondary infections	Limited metabolic recovery; decreased protein synthesis capacity	[44,45]
>96 h	Chronic immune exhaustion/death risk phase	Irreversible multiple organ damage; coexistence of inflammation and metabolic abnormalities	Exhaustion of immune memory cells; diminished reactivation capability	Mitochondrial inactivation; lipid accumulation; impaired glucose utilization	[44]

the development of MODS.⁵⁴ Distinct metabolic profiles of immune cell subsets are closely tied to their functional states and may drive the progression of MODS.^{55,56} The metabolic adaptations support effector functions and determine the direction of the immune response (pro-inflammatory vs immunosuppressive), as a core mechanism in the evolution of MODS.^{6,57}

In established animal models of sepsis, the initial pro-inflammatory phase is characterized by a metabolic shift toward glycolysis, which supports rapid immune cell activation and effector function. Emerging evidence highlights the role of glycolysis-related pathways, such as the lactate-ROS axis and spinster homolog 2 (Spns2)/sphingosine-1-phosphate (S1P) signaling (a regulation of extracellular signaling), in modulating inflammatory responses and maintaining immune homeostasis during early sepsis, thereby limiting both hyperinflammation and subsequent immunosuppression.⁵⁸ Notably, pharmacological inhibition of glycolysis has been associated with improved survival in LPS models.⁵⁹ As sepsis progresses, mitochondrial dysfunction,⁶⁰ collapse of cellular energy metabolism,⁶¹ and immune exhaustion⁶² act as dominant features, collectively contributing to the development of MODS.^{63–65} While the preceding table summarizes the parallel immune and metabolic states observed at different stages of CLP-induced sepsis, the molecular underpinnings of the immunometabolic transition remain incompletely understood and require further elucidation.

At the early stage of septic stimulation, the host rapidly mounts a robust immune response, characterized by extensive recruitment and activation of immune cells. Classic immune cell types, including T cells, B cells, natural killer (NK) cells, and various myeloid populations, undergo significant phenotypic alterations and display pronounced heterogeneity.⁶⁶ The dynamic immune landscape is accompanied by a marked elevation of pro-inflammatory cytokines in the peripheral blood, such as TNF- α , IL-1 β , IL-6, and IFN- γ .^{17,67} The early inflammatory events reflect the systemic nature of immune activation and contribute to the progression of immunopathology in sepsis.

Specifically, macrophages exhibit enhanced glycolysis during sepsis, leading to elevated lactate production, which facilitates rapid energy supply necessary to sustain phagocytic activity and inflammatory responses.^{47,68} The metabolic reprogramming is accompanied by the activation of key signaling pathways across various organs, including HIF-1 α ,⁶⁹ mTOR,⁷⁰ and NF- κ B.⁷¹ The metabolic reprogramming of macrophages associated with the relevant signals under pro-inflammatory and anti-inflammatory conditions are illustrated in Figure 2. In the hypoxic and inflamed microenvironment

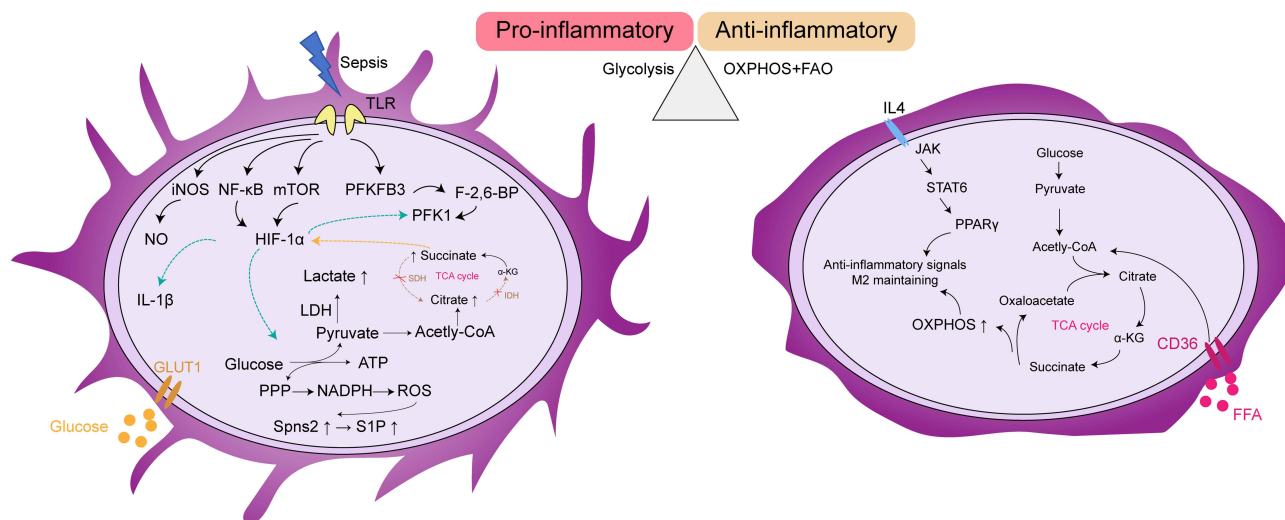


Figure 2 Distinct metabolic programs in pro-inflammatory and anti-inflammatory macrophage phenotypes. The metabolic reprogramming of macrophages under pro-inflammatory (left) and anti-inflammatory (right) conditions. In the pro-inflammatory state induced by sepsis, glycolysis is upregulated via toll-like receptor (TLR)-mediated signaling pathways, leading to increased inducible nitric oxide synthase (iNOS) expression, NF- κ B activation, mTOR signaling, and hypoxia-inducible factor-1 α (HIF-1 α). It results in elevated lactate production, accumulation of succinate, and activation of the pentose phosphate pathway (PPP), collectively promoting reactive oxygen species (ROS) generation and pro-inflammatory cytokine release (eg, IL-1 β). In the anti-inflammatory state driven by IL-4 stimulation, oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) are enhanced through the JAK-STAT6-PPAR γ axis, maintaining M2 macrophage polarization and anti-inflammatory functions.

Abbreviations: ATP, Adenosine triphosphate; α -KG, Alpha-ketoglutarate; CD36, Cluster of differentiation 36; FAO, Fatty acid oxidation; F-2,6-BP, Fructose-2,6-bisphosphate; FFA, Free fatty acid; HIF-1 α , Hypoxia-inducible factor 1-alpha; IL-1 β , Interleukin-1 beta; IL-4, Interleukin-4; iNOS, Inducible nitric oxide synthase; JAK, Janus kinase; LDH, Lactate dehydrogenase; mTOR, Mechanistic target of rapamycin; NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; OXPHOS, Oxidative phosphorylation; PFK1, Phosphofructokinase-1; PFKFB3, 6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PPAR γ , Peroxisome proliferator-activated receptor gamma; PPP, Pentose phosphate pathway; ROS, Reactive oxygen species; S1P, Sphingosine-1-phosphate; Spns2, Spinster homolog 2 (sphingolipid transporter); STAT6, Signal transducer and activator of transcription 6; TCA cycle, Tricarboxylic acid cycle; TLR, Toll-like receptor.

induced by sepsis, stabilization of HIF-1 α promotes the expression of key glycolytic enzymes and downregulates OXPHOS, thereby accelerating glucose metabolism. The process drives macrophage polarization toward the pro-inflammatory M1 phenotype, characterized by increased secretion of cytokines such as TNF- α and IL-1 β .⁷² Mechanistically, HIF-1 α regulates the transcription of multiple glycolytic enzymes such as phosphofructokinase (PFK), increases the expression of glucose transporter 1 (GLUT1) to enhance glucose uptake, inhibits pyruvate entry into mitochondria (which would otherwise fuel OXPHOS), and promotes the conversion of pyruvate to lactate through upregulation of lactate dehydrogenase (LDH). Moreover, the mTORC1-HIF-1 α axis is essential for cytokine production and the upregulation of costimulatory molecules CD80 and CD86 in dendritic cells (Jantsch et al, 2008). Thus, modulation of glycolysis and macrophage polarization has emerged as a potential therapeutic avenue in sepsis. For example, the Krüppel-like transcription factor KLF14 has been shown to exert protective effects in septic mice by suppressing the transcription of Hexokinase 2, thereby reducing glycolytic flux and the release of inflammatory cytokines in macrophages.⁷³ Promoting autophagy in alveolar macrophages via the RAGE/PI3K/AKT/mTOR pathway can inhibit NLRP3 inflammasome activation, exerting anti-inflammatory and lung-protective effects.⁷⁴ Furthermore, the Sphingosine kinase 1 (S1P)/Sphingosine-1-phosphate receptor 3 (S1PR3) signaling axis modulates macrophage polarization and the Warburg effect during sepsis, thereby alleviating excessive inflammation and multi-organ failure.⁷⁵ Collectively, these findings highlight macrophages as promising targets for therapeutic intervention in sepsis.

In both CLP and LPS models, neutrophil metabolic reprogramming is characterized by enhanced glycolysis, increased oxidative stress, and mitochondrial ROS involvement in signaling regulation.^{76,77} Fatty acids are utilized during developmental stages, while glucose uptake is elevated via upregulation of GLUT1, supporting aerobic glycolysis and redirection toward the pentose phosphate pathway (PPP).⁷⁸ The processes are essential for chemotaxis, oxidative burst, and neutrophil extracellular traps (NETs) formation and release, which are central to neutrophil-mediated local pathogen control. NETs, an immune defense mechanism, trap and kill pathogens to restrict dissemination, and rely on glycolysis as their main energy source.⁷⁹ NETs also regulate METTL3-m6A-IGF2BP2-dependent m6A modification of HIF-1 α , promoting metabolic reprogramming and ferroptosis in alveolar epithelial cells.⁷⁶ However, excessive polymorphonuclear neutrophil (PMN) recruitment or NETs formation could drive MODS. Interaction between macrophages and neutrophils further shapes immune signaling in sepsis. For instance, M2-Exos promote LXA4 production, downregulate C-X-C Motif Chemokine Receptor 2 (CXCR2) and ROS, thereby inhibiting neutrophil function. Neutrophil-derived exosomal miR-30d-5p induces M1 macrophage polarization and pyroptosis via NF- κ B activation, aggravating sepsis-related acute lung injury.⁸⁰ Beyond macrophages, CD4⁺ T lymphocytes may support early bacterial clearance by modulating neutrophil function, possibly via an IFN- γ -dependent mechanism.⁸¹

Deficiency of Adenosine 5'-monophosphate (AMP) -activated protein kinase (AMPK) enhances pyruvate kinase M2 (PKM2)-dependent aerobic glycolysis, leading to the release of high mobility group box 1 (HMGB1), a late mediator of lethal systemic inflammation, in macrophages and monocytes. Activation of AMPK could protect mice from endotoxin shock and polymicrobial sepsis, whereas depletion of AMPK α in myeloid cells promotes disease progression. Moreover, inhibition of PKM2 reduces lactate production, HMGB1 release, and sepsis-related mortality in AMPK α -deficient mice. These findings suggest that disruption of AMPK-dependent immunometabolic pathways may contribute to the development of sepsis and represent a potential target for therapeutic intervention.⁸²

Sepsis, as a systemic inflammatory condition, induces extensive metabolic reprogramming across diverse immune cell populations. Macrophages and neutrophils exhibit well-characterized metabolic changes, while other immune cells such as lymphocytes, dendritic cells, granulocytes, and innate lymphoid cells also show notable functional impairments and metabolic alterations. The immune disturbances contribute to a shift from effective antimicrobial defense toward immune dysfunction, sustained inflammation, and progressive organ damage. Despite growing interest in immunometabolism, the metabolic remodeling of many of these cell types remains poorly understood. Elucidating the relationship between immune cell metabolism and function in sepsis may uncover novel targets for therapeutic intervention.

Around 48 hours after CLP, the host gradually enters an immunosuppressive state, characterized by functional exhaustion, reduced numbers, or depletion of multiple immune cell types, which results in diminished antimicrobial capacity and increased susceptibility to secondary infections and MODS. For instance, CLP mice exhibit a decreased proportion of innate immune cells and macrophages in the bone marrow, along with an increased proportion of T lymphocytes.⁸³

In macrophages, inhibition of the interaction between NF- κ B p65 and nuclear factor of activated T-cells 5 could regulate the expression of glycolytic genes and proinflammatory cytokines in immunosuppressive macrophages, thereby promoting a favorable outcome in sepsis.⁸⁴ Moreover, Mdivi-1, a mitochondrial fission inhibitors alleviates sphingosine-1-phosphate receptor 2 (S1PR2)-induced macrophage immunosuppression and improves outcomes in CLP mice by inhibiting Drp1-dependent mitochondrial fragmentation in macrophages.⁸⁵

Sepsis-associated sickness behaviors include anorexia, lethargy, altered sleep patterns, and social withdrawal. The systemic mediators involved include adrenal hormones,⁸⁶ bile acids (BAs),⁸⁷ adenosine, and microbiota-derived metabolites, especially short-chain fatty acids (SCFAs).⁸⁸ Other studies have demonstrated that fasting-induced metabolic programs exert beneficial effects during severe infections.⁸⁹ Fasting regulates leukocyte distribution by promoting monocyte homing to the bone marrow;⁹⁰ while refeeding leads to a surge of circulating monocytes, which may cause tissue damage in the context of antibacterial host responses.⁹¹ It is relevant to sepsis experimental models, since cecal necrosis and leakage, anorexia, and persistent weight loss are characteristic manifestations. Metabolic reprogramming of B cells during sepsis increases ATP production, which is converted to adenosine by CD39 on plasma cells, impairing macrophage bactericidal activity and enhancing IL-10 production, thereby increasing the risk of recurrent infections.⁹²

After LPS stimulation, neutrophils differentiate into multiple subsets that exhibit distinct functional impairments during late sepsis, including inhibition of apoptosis, severe impairment of chemotaxis, and widespread tissue infiltration. LPS mediates programmed death-ligand 1 (PD-L1) overexpression, an immune suppression signal, in neutrophils via the p38 α -mitogen- and stress-activated protein kinase 1, (MSK1)/-MAPK-activated protein kinase 2 (MK2) pathway. The PD-L1 high subset exerts immunosuppressive effects in a direct contact-dependent manner, including inhibition of T cell activation and induction of T cell apoptosis and transdifferentiation. The process is driven by metabolic reprogramming of neutrophils from mitochondrial oxidative phosphorylation to glycolysis, providing energy and metabolic substrates (eg acetyl-CoA for histone acetylation) necessary for rapid expression of immune regulatory molecules like PD-L1.⁹³

Single-cell resolution sequencing of clinical samples have identified distinct immune cell clusters associated with Persistent Inflammation- Immunosuppression-Catabolism Syndrome (PICS) in sepsis. The clusters show unique phenotypic and functional features of diverse immune cell subsets, including monocytic myeloid-derived suppressor cell-like monocytes, B cells, regulatory T cells, and megakaryocytes.⁴⁵ Moreover, sepsis-induced immunosuppression is closely linked to the depletion of immature dendritic cells. For example, newly formed immature respiratory dendritic cells are locally programmed by residual inflammatory immune alarms to produce increased IL-10, thereby promoting tolerance.⁹⁴

However, the distinct metabolic changes and their downstream cascades in specific immune cell populations within experimental sepsis models still require further investigation, as immune cell metabolism reflects their functional state as well as serves as a regulatory causal mechanism. Based on the restoring metabolic homeostasis, such as enhancing mitochondrial function, supplementing NAD⁺, and modulating the balance between glycolysis and lipid metabolism, has long been considered a potential therapeutic strategy to reverse immunosuppression and improve prognosis.

Immunometabolic Alterations Leading to Organ Injuries and Inter-Organ Crosstalk

In the early stage of sepsis, immune cell metabolism shifts toward glycolysis. Although the metabolic reprogramming facilitates rapid pathogen clearance in the short term, its sustained activation and dysregulation leading to abnormal accumulation of metabolic byproducts and a cytokine storm. The process is initiated by inflammasome activation and a robust pro-inflammatory response, characterized by the release of IL-6, TNF- α , and IFN- γ , along with activation of the coagulation system.⁶ The metabolically inflammatory and toxic substance propagates through the bloodstream to distant organs, inducing mitochondrial dysfunction, oxidative stress, and programmed cell death, ultimately leading to MODS.⁹⁵

Organ-Specific Metabolic Dysregulation and Injuries

During the progression of sepsis, organs such as heart, lungs, kidneys, brain, and liver become high-risk targets of injuries, exhibiting complex and intertwined patterns of functional impairment. The organ injuries result from cascades of inflammatory cytokines, oxidative stress, and coagulation activation, also closely related to organ-specific changes in the

immune microenvironment. Pathological manifestations such as cardiac dysfunction, acute respiratory distress syndrome (ARDS), acute kidney injury, hepatocyte apoptosis, and brain dysfunction collectively form the anatomical basis for the high mortality rate of sepsis (Figure 3). A deeper understanding of these inter-organ injuries and their crosstalk mechanisms should provide theoretical foundations and clinical directions for precision interventions and organ-protective strategies in sepsis.

In septic cardiomyopathy, infiltrating macrophages and cardiomyocytes undergo metabolic reprogramming toward glycolysis, accompanied by decreased mitochondrial oxidative phosphorylation capacity, lactate accumulation, and redox imbalance. The metabolic alterations lead to insufficient energy supply and calcium handling abnormalities, thereby triggering septic myocardial dysfunction. Specifically, CLP mice exhibit significant cardiac dysfunction, altered mitochondrial dynamics, reduced cardiac lipid and glucose uptake, impaired fatty acid and glucose oxidation, enhanced myocardial glycolysis, and decreased ATP production.⁹⁶ The metabolic changes result in CLP-induced interstitial fibrosis, cardiac dysfunction (manifested as reduced ejection fraction, fractional shortening, shortening/relengthening velocity, peak shortening, and electrically stimulated intracellular Ca^{2+} rise, alongside increased left ventricular end systolic diameter and relengthening duration), superoxide (O_2^-) buildup, apoptosis, necroptosis, and ferroptosis characterized by downregulated glutathione peroxidase 4 (GPX4) and SLC7A11.⁹⁷

Improving mitochondrial dysfunction could partially alleviate septic cardiomyopathy. In CLP mice, cardiac TLR4-extracellular signal-regulated kinase1/2-dynamain-related protein 1 is activated, leading to mitochondrial fission and dysfunction, leading to cardiac dysfunction, cardiomyocyte apoptosis, recruitment of Mac-2⁺ macrophages, production of superoxide, and pro-inflammatory cytokines.⁹⁸ Growth arrest-specific 6, an immune homeostasis regulator, alleviates mitochondrial damage, endoplasmic reticulum stress, oxidative stress, and apoptosis through an NLRP3 inflammasome-dependent mechanism, ultimately improving cardiac dysfunction in CLP mice.⁹⁹

The lung is one of the earliest organs affected in sepsis. In CLP mice, lung injury scores, lung tissue wet-to-dry weight ratios, pulmonary vascular permeability, and levels of inflammatory cytokines including IL-1 β , TNF- α , IL-6, IFN- γ , and C-C motif chemokine ligand 3 (CCL3) in bronchoalveolar lavage fluid and lung tissue are all elevated, eventually leading to ARDS.¹⁰⁰ The process, similar to that occurring in the heart, begins with immune cells releasing large amounts of ROS and pro-inflammatory cytokines, resulting in disruption of the alveolar-capillary barrier. Meanwhile, pulmonary capillary endothelial cells can be divided into distinct subpopulations, such as Plat⁺ capillaries which interact with neutrophils via intercellular adhesion molecule-1 (ICAM-1) adhesion and participate in innate immune responses, and CD74⁺ capillaries that express high levels of major histocompatibility complex (MHC) proteins (an antigen presenting protein) and engage with T cells in adaptive immunity.¹⁰¹ Overall, oxygen consumption in the lung increases, but oxygen utilization efficiency declines, impairing gas exchange function and eventually progressing to acute lung injury or ARDS.¹⁰⁰ In the context, inhibition of the macrophage MAPK signaling negative feedback regulator Sprouty4 (Spry4) alleviates inflammation, oxidative stress, and acute lung injury in CLP mice.¹⁰² Additionally, lactate accumulated during sepsis promotes acetylation of cold-inducible RNA-binding protein (CIRP) in macrophages, leading to CIRP release, which is internalized by pulmonary vascular endothelial cells (PVECs) via TLR4-mediated endocytosis, exacerbating acute lung injury.¹⁰³ Moreover, ferroptosis, a programmed cell death process characterized by iron-dependent lipid peroxidation, which is highly dependent on cellular metabolic states, plays a crucial role in lung injuries. Exosome-mediated signaling between macrophages and pulmonary vascular endothelial cells is pivotal in sepsis-induced acute lung injury, with the guanylate-binding protein 2 (GBP2)- OTU deubiquitinase 5 (OTUD5)-GPX4 axis identified as a driver of endothelial ferroptosis and lung damage.¹⁰⁴ Activation of the Sirtuin 1 (SIRT1)/NADPH oxidase 4 (NOX4) signaling pathway inhibits ferroptosis, thereby mitigating sepsis-induced damage to the lung microvascular endothelial barrier.¹⁰⁵

The liver plays a central role in regulating systemic inflammation and metabolism. Kupffer cells, the liver-resident tissue macrophages, act as a crucial component of the innate immune system. Excessive pro-inflammatory activation of Kupffer cells is a key pathogenic mechanism underlying sepsis-induced liver injury. During sepsis, Kupffer cells undergo pronounced phenotypic switching and functional reprogramming, including enhanced innate antibody/complement-dependent clearance, TLR13-mediated protective cell regeneration, and immunometabolic changes regulated by mitochondrial function.¹⁰⁶ Treatment with the mitochondrial fission inhibitor Mdivi-1 alleviates CLP-induced liver injury and improves liver pathology and function.⁴³ Extracellular CIRP (eCIRP) promotes M1 polarization of Kupffer cells via the

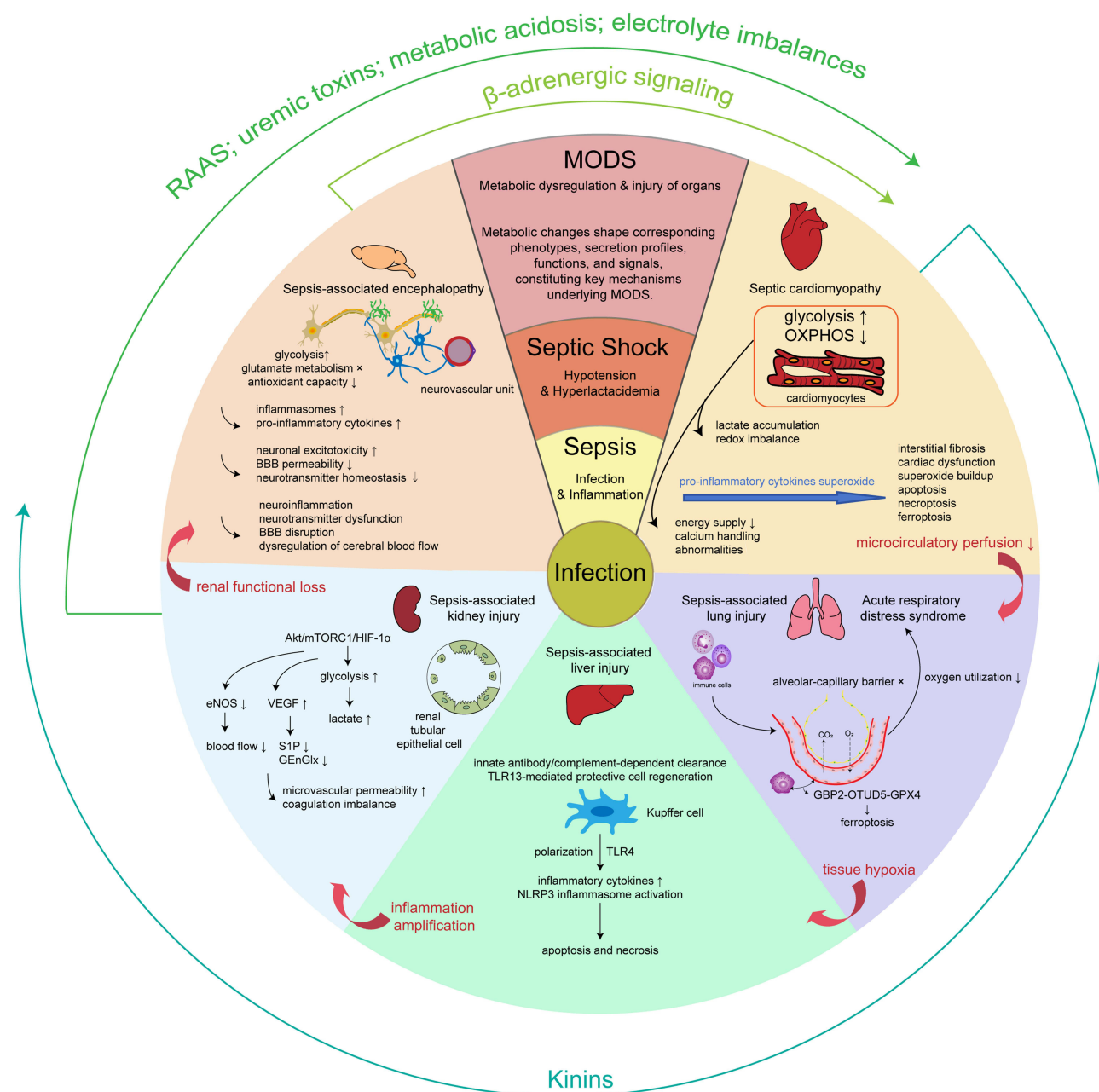


Figure 3 Organ-specific injury during sepsis progression. Sepsis-associated organ dysfunction involves disruption of inter-organ crosstalk, where organs form a complex crosstalk network mediated by metabolic products, inflammatory mediators, and immune signals. Metabolic reprogramming is associated with tissue hypoxia, microcirculatory dysfunction, mitochondrial impairment, oxidative stress, and inflammatory amplification, leading to sepsis-associated injuries in the brain, heart, lungs, kidneys, and liver. Key processes include glycolytic shift and accumulation of lactate. Interactions between organs are modulated by systemic factors such as renin-angiotensin-aldosterone system (RAAS) activation, β -adrenergic signaling, kinin release, uremic toxin accumulation, metabolic acidosis, and electrolyte imbalances. It was emphasized that augmented glycolysis, attenuated OXPHOS, and lactate accumulation were universal metabolic features observed across affected organs and immune cell populations. During the progression of sepsis, the detrimental impact of cardiac injury was the reduction of microcirculatory perfusion; pulmonary injury resulted in tissue hypoxia; hepatic injury contributed to inflammation amplification; renal injury led to renal functional loss, including metabolic and homeostatic disturbances caused by reduced glomerular blood flow and coagulation imbalance. Within the central nervous system, SIRS gave rise to diffuse cerebral dysfunction. The above processes were denoted by red arrows. Arrows projecting outward from each organ depicted inter-organ/system crosstalk signals. The regulation of cardiac output was mediated via the β -adrenergic system of nervous system. In the kidney, renin release from the juxtaglomerular apparatus activated the RAAS to elevate blood pressure, although chronic activation predisposed to heart failure. In the setting of impaired renal excretion, accumulation of protein metabolites and gut-derived toxins contributed to cardiomyopathy. Furthermore, metabolic acidosis and electrolyte imbalances caused by renal dysfunction reduced myocardial contractility. Under conditions of myocardial ischemia or stress, kinins exerted cardioprotective effects, improved myocardial perfusion, while its vasodilatory and permeability-enhancing actions, together with its role in modulating inflammation, further affected other organs.

Abbreviations: 4E-BP1, Eukaryotic translation initiation factor 4E-binding protein 1; α -KG, Alpha-ketoglutarate; Akt, Protein kinase B; BBB, Blood-brain barrier; eNOS, Endothelial nitric oxide synthase; GBP2, Guanylate-binding protein 2; GEnGlx, Endothelial glycocalyx; GPX4, Glutathione peroxidase 4; HIF-1 α , Hypoxia-inducible factor 1 α ; mTORC1, Mechanistic target of rapamycin complex 1; MTORC1, Mechanistic target of rapamycin complex 1; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; OTUD5, OTU deubiquitinase 5; RAAS, Renin-angiotensin-aldosterone system; S1P, Sphingosine-1-phosphate; TLR13, Toll-like receptor 13; TLR4, Toll-like receptor 4; VEGF, Vascular endothelial growth factor.

TLR4 pathway, resulting in excessive production of inflammatory cytokines.¹⁰⁷ Proteomic and metabolomic analyses of LPS mice liver identified recombinant erythrocyte membrane protein 4.2 (Epb42) and adenosine diphosphate (ADP) as potential key proteins and metabolites driving sepsis-related acute liver injury. Epb42 is a red blood cell membrane skeletal protein involved in maintaining erythrocyte shape and elasticity. Under the hyperinflammatory state of sepsis, impaired erythrocyte deformability and microcirculatory obstruction suggest sinusoidal microcirculatory perfusion dysfunction, exacerbating hepatocyte hypoxia and necrosis. ADP is a critical platelet activation signal molecule that induces platelet aggregation and participates in microthrombosis. Increased ADP release activates sinusoidal endothelial cells and Kupffer cells, worsening hepatic microvascular inflammation and thrombosis, and triggering NLRP3 inflammasome activation to amplify inflammatory responses, leading to hepatocyte apoptosis and necrosis.⁴³ However, it is noteworthy that current studies predominantly focus on hepatic phenotypes and pathological changes, with relatively few investigations addressing the metabolic alterations of Kupffer cells and other immune cells and their relationship to functional outcomes, which highlights an important direction for future research.

The spleen serves as a vital immunological organ during sepsis, contributing to both antigen clearance and the regulation of immune homeostasis. In experimental models of sepsis, the spleen exhibits marked structural damage and metabolic reprogramming. As early as 6 hours after sepsis onset, CD4⁺ T cells in the spleen display distinct transcriptional changes involving T-cell receptor and MAPK signaling pathways, indicating high sensitivity to inflammatory stimuli.¹⁰⁸ The splenic interstitial fluid becomes hyperosmotic and its protein composition disrupted, reflecting structural alterations in the local microenvironment in CLP mice.¹⁰⁹ As sepsis progresses, immunological dysregulation in the spleen is characterized by increased lymphocyte apoptosis, macrophage dysfunction, and Th1/Th2 imbalance.¹¹⁰ Following acute infection, the accumulation of Siglec-F⁺ neutrophils in the spleen induces the expression of immunosuppressive markers such as PD-1 and lymphocyte-activation gene 3 on T cells, implicating these cells as critical mediators of sepsis-induced immunosuppression. These neutrophils modulate T cell function through cell-to-cell contact and anti-inflammatory cytokines (eg IL-10), serving as key drivers of late-stage sepsis-induced immune paralysis.¹¹¹ Raman spectroscopy reveals enhanced DNA activity in splenic T lymphocytes within 24 hours of acute inflammation, suggesting a peak in transcriptional activity.¹¹² Moreover, the spleen acts as an extramedullary site of thrombopoiesis under septic conditions, where IL-3 drives the differentiation of myeloid progenitors into megakaryocytes that produce immunomodulatory CD40L⁺ platelets, contributing to host defense and improved survival.¹¹³ At the metabolic level, splenic immune cells undergo enhanced glycolysis alongside mitochondrial dysfunction. In LPS-challenged mice, activating transcription factor 4 (ATF4) plays a central role in glycolytic activation, promoting pro-inflammatory responses and alleviating macrophage tolerance during sepsis.⁶¹ In the spleens of CLP mice, diminished expression of sterile α and HEAT/armadillo motif-containing protein (SARM), a regulator of immune cell apoptosis, is associated with caspase-3 cleavage and ATP depletion, indicating mitochondrial failure and enhanced apoptosis.¹⁰³ Furthermore, alpha-ketoglutaric acid (AKG), a key intermediate in the tricarboxylic acid cycle, has been shown to attenuate oxidative stress, restore mitochondrial membrane potential, and balance mitochondrial dynamics (promoting fusion and inhibiting excessive fission) in the spleen of LPS piglets, which enhances autophagic activity in splenic macrophages by modulating mTOR signaling and LC3B expression, thereby alleviating functional impairment in splenic tissues.⁶⁷

Acute kidney injury (AKI) is a common and severe complication of sepsis, characterized by significant morbidity and mortality. During sepsis, both inflammatory cells and renal parenchymal cells, including macrophages, neutrophils, and renal tubular epithelial cells, undergo metabolic shifts toward aerobic glycolysis to amplify pro-inflammatory responses and enhance cellular tolerance to septic insults. As the disease progresses, these cells revert to OXPHOS, promoting anti-inflammatory responses and facilitating functional recovery. Changes in mitochondrial dynamics and metabolic reprogramming are central to the energy alterations occurring during septic AKI.¹¹⁴ Mitophagy, the selective degradation of damaged mitochondria, has been proved to confer protective effects against AKI via the PTEN-induced kinase 1- parkin RBR E3 ubiquitin protein ligase pathway, where optineurin functions act as an adaptor protein for mitophagy.¹¹⁵ Within the context of septic AKI, immunosuppression manifests as an enhanced anti-inflammatory phenotype with lactate, an end product of glycolysis, playing a key role. Lactate transcends its traditional role as a mere metabolic byproduct to function as an important signaling molecule. Specifically, lactate inhibits TLR4-mediated signaling to mitigate inflammation, thereby promoting M2 macrophage polarization and reducing LPS-induced NF- κ B activation. Additionally,

lactate affects immune cell migration and cytokine production through export via the monocarboxylate transporter 4. It also triggers “stop migration” signals via lactate transporters SLC5A12 in CD4⁺ T cells and SLC16A1 in CD8⁺ T cells.¹¹⁴ Renal tubular epithelial cells respond similarly to immune cells by activating aerobic glycolysis via the Akt/mTORC1/HIF-1 α signaling pathway, which promotes the conversion of pyruvate to lactate and, together with pyruvate dehydrogenase kinase (PDHK), inhibits lactate conversion to acetyl-CoA, thereby reducing OXPHOS and related metabolic processes.^{116,117} Reduced glomerular blood flow attribute to inhibition of endothelial nitric oxide synthase activity in the arteries and glomeruli, while decreased cortical peritubular capillary perfusion is associated with epithelial oxidative stress. Elevated levels of the vascular endothelial growth factor system, decreased circulating sphingosine-1-phosphate, and loss of glomerular endothelial glycocalyx components contribute to increased microvascular permeability. Coagulation imbalances occur across all microvascular segments, representing a significant cause of renal functional loss.¹¹⁸

Sepsis-associated encephalopathy (SAE) is a diffuse brain dysfunction caused by sepsis, presenting with a spectrum of neurological abnormalities ranging from delirium to coma. It is a relatively common complication of sepsis and is associated with poor patient prognosis and high mortality. The pathogenesis involves neuroinflammation, neurotransmitter dysfunction, blood-brain barrier (BBB) disruption, and dysregulation of cerebral blood flow. Notably, astrocytes and microglia undergo metabolic reprogramming characterized by enhanced glycolysis, disrupted glutamate metabolism, and impaired antioxidant capacity. The process activates inflammasomes and leads to the release of pro-inflammatory cytokines such as IL-1 β and TNF- α , contributing to increased neuronal excitotoxicity. BBB permeability increases and neurotransmitter homeostasis is disturbed.¹¹⁹ Importantly, inflammation in SAE results from systemic metabolic, inflammatory, and hemodynamic dysregulation driven by SIRS, rather than direct central nervous system infection.¹²⁰ Although the brain itself is not infected, peripheral inflammatory signals would induce widespread neuroinflammation through neural and humoral pathways, ultimately causing neuronal damage.¹²¹ Similar to other immune cells, microglia shift their metabolism from OXPHOS-dominated homeostasis to glycolysis upon septic stimulation. The metabolic switch rapidly meets the energy demands for microglial proliferation, migration, cytokine secretion, and phagocytosis, despite glycolysis being less efficient than OXPHOS. Restoring mitochondrial function and reducing inducible nitric oxide synthase (iNOS) expression could recover impaired brain function.¹²² The latter is highly expressed in activated glial cells, producing high concentrations of nitric oxide (NO) that damage neuronal mitochondria and membrane structures, inhibit mitochondrial complex IV (cytochrome c oxidase), and perpetuate a vicious cycle, which also compromise the BBB and promote infiltration of inflammatory cells into the brain.¹²³

In summary, immunometabolic reprogramming in experimental sepsis models exhibits overall similarity, with a core feature being a metabolic switch characterized by enhanced glycolysis, impaired mitochondrial activity, and close association with hypoxia-inducible factors and lactate production. It underlies why lactate has served as a clinical biomarker for sepsis over several decades. Changes in immune cell metabolism influence corresponding phenotypes, secretion profiles, clearance functions, and distribution of metabolic products. During the hyperinflammatory phase, these changes induce acute organ damage, while in the immunosuppressive phase, they inhibit tissue repair and exacerbate secondary injuries, representing one of the key mechanisms driving the development and progression of MODS. Therefore, precise intervention targeting immunometabolic processes may represent a promising strategy to improve organ dysfunction in sepsis in the future.

Inter-Organ Crosstalk in Sepsis

Sepsis-associated organ dysfunction involves disruption of inter-organ crosstalk, where organs form a complex crosstalk network mediated by metabolic products, inflammatory mediators, and immune signals. The network collectively drives or mitigates the progression of MODS. For example, injuries in one organ can initiate vicious cycles that exacerbate MODS and cause secondary damage or dysfunction in other organs.¹²⁴ Although the multi-organ axes influenced by the gut microbiota have been extensively investigated in various disease contexts, the precise mechanisms underlying the inter-organ crosstalk remain incompletely understood.

The cardiovascular, respiratory, and renal systems are closely interconnected and interdependent, with management of cardiovascular dysfunction often focusing on regulating blood pressure and ensuring adequate organ perfusion. For

example, refractory hypotension is a hallmark of septic shock. During the process, multiple neuroendocrine mechanisms are activated, such as the renin-angiotensin-aldosterone system (RAAS) and the β -adrenergic nervous system, to maintain cardiac output under decompensated cardiovascular function.¹²⁵ Additionally, kinins synthesized and secreted by the heart may play a significant role in modulating communication between the cardiovascular system and other organs during sepsis.^{126,127} Upregulation of TNF- α and IL-6, along with increased levels of uremic toxins such as indoxyl sulfate, are critical mediators of the impact of AKI on distant organs.¹²⁸ The alterations affect the heart, lungs, central nervous system, hematologic system, liver, gut, and microbiome.¹²⁹ Furthermore, volume overload, retention of uremic toxins, and excessive activation of the RAAS system due to AKI accelerate heart failure. Accumulation of uremic toxins, metabolic acidosis, and electrolyte imbalances contribute to cardiovascular toxicity and may increase the risk of myocardial ischemia and life-threatening arrhythmias.¹³⁰ The development of ARDS in sepsis, characterized by diffuse pulmonary inflammation and edema leading to acute respiratory failure, cannot be fully explained by cardiac failure or fluid overload alone. ARDS may result from infection itself or from systemic inflammation.¹³¹

Whether in clinical sepsis patients or in the CLP model, differences exist in the microbial composition between the healthy state and sepsis conditions, characterized by the loss of beneficial microbiota and the overgrowth of potential pathogens. *Enterococcus*, *Klebsiella*, and *Enterobacteriaceae* were observed to be enriched in both clinical samples and the CLP model. *Enterococcus* showed positive correlations with a greater number of genes associated with cell chemotaxis and inflammatory damage, while displaying negative correlations with a larger set of genes involved in lipid metabolism.³⁰ *Enterococcus* is also known to reshape the gut's metabolic environment via the arginine deiminase pathway, thereby promoting the growth of various pathogens, such as *Escherichia coli* and *Clostridioides difficile*, and potentially contributing to secondary infections.^{132,133} In addition, *Bacteroides* has been identified as a key bacterium associated with adverse outcomes in sepsis, affecting gut barrier permeability or H₂S production during the course of the disease. The decrease in gut bacterial diversity is reflected by a marked depletion and alteration of intestinal metabolites, where metabolites involved in aromatic amino acid metabolism are the most severely affected.¹³⁴ Tryptophan can also be metabolized by various gut microbes into indole derivatives, which are capable of activating the aryl hydrocarbon receptor (AhR) or pregnane X receptor (PXR) in intestinal epithelial cells or lymphocytes, thereby promoting anti-inflammatory responses, antimicrobial peptide secretion, and xenobiotic metabolism.¹³⁵ Following gut barrier disruption, do the composition and metabolism of intestinal microbiota change, but the microbial barrier also becomes disorganized, losing its protective function. When gut microbes and their products, such as LPS and peptidoglycan, enter the portal circulation, they further exacerbate hepatic burden and inflammatory responses. Impaired circulatory perfusion, subsequent ischemia, inflammatory injury, and neuroendocrine dysregulation act in concert, ultimately leading to gut barrier failure.¹³⁶ The process subsequently induces secondary alterations in the gut microbiota production of bioactive mediators, including short-chain fatty acids (acetate, propionate, and butyrate), succinate, and serotonin, which exert systemic effects on distant organs and modulate inflammatory signaling pathways.¹³⁷

Given the characteristic gut barrier disruption in the CLP model and the pronounced gastrointestinal alterations observed in clinical sepsis patients, the “gut-X” axes have become a central focus and hotspot in sepsis research, including the Gut-Liver Axis, Gut-Brain Axis, Gut-Lung Axis, Gut-Kidney Axis, Gut-Heart Axis, Gut-Immune Axis, and Gut-Liver-Brain Axis, emphasizing the bidirectional regulatory interactions between the gut and distal organs or systems. Among these, the Gut-Liver-Brain Axis, as a composite axis, highlights the intricate interplay between the gut microbiota and barrier, hepatic immune and metabolic functions, inflammatory mediators and metabolites, and the nervous system, and is increasingly being investigated. The axis is particularly relevant for patients with cognitive dysfunction and poor long-term outcomes. Under physiological conditions, the gut microbiota-liver-brain axis maintains homeostasis through bidirectional communication; however, in sepsis, The network is disrupted. Such disruption exacerbates gastrointestinal and hepatic dysfunction but also contributes to cognitive impairment and severe disease progression.⁴⁹

The liver is a key regulator of systemic homeostasis, responsible for the clearance of metabolic byproducts, modulation of immune responses, and secretion of hepatokines. During sepsis, disruption of the gut barrier and dysbiosis facilitate the translocation of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) to the liver and systemic circulation. The liver plays a critical role in modulating immune defense during systemic infection through mechanisms including bacterial clearance, lipopolysaccharide detoxification, release of

cytokines and acute-phase proteins, and regulation of inflammatory metabolism.¹³⁸ Under physiological conditions, small amounts of intestinal LPS passing through the portal vein are processed and detoxified by the liver. When sepsis-induced inflammation and circulatory disturbances exceed the liver capacity, the defensive intraluminal mechanisms that prevent massive LPS translocation into the systemic circulation gradually fail.¹³⁹ Lipopolysaccharide-binding protein (LBP) binds to the lipid A moiety of LPS, forming an LPS-LBP complex, which is recognized by TLR4 and myeloid differentiation factor 2 (MD-2), thereby triggering a cascade of inflammatory responses. In addition, gut-derived PAMPs and DAMPs may serve as key triggers, leading to dysregulated immune responses or excessive inflammation, impaired hepatic clearance of pathogenic bacteria, and metabolic disturbances.¹³⁸ For example, the accumulation of metabolites such as lactate, ammonia, and bilirubin in the circulation can lead to hepatic encephalopathy and hepatorenal syndrome. Cytokine storms and immune dysregulation may precipitate acute respiratory distress syndrome. Abnormalities in coagulation factors and the fibrinolytic system can result in disseminated intravascular coagulation, impaired microcirculatory perfusion in the kidney, lung, and brain, and ischemic tissue injury. In summary, these inter-organ crosstalk mechanisms contribute to cardiovascular dysfunction, systemic inflammation, and insulin resistance, thereby accelerating the progression of MODS.¹⁴⁰

Within the Gut-Liver-Brain Axis, neural, endocrine, and immune pathways constitute a network that mediates bidirectional communication and regulation with the central nervous system. Hepatic vagal sensory afferent nerves indirectly sense the gut microenvironment and transmit these sensory signals to the nucleus tractus solitarius in the brainstem, ultimately influencing vagal parasympathetic nerves and enteric neurons. Surgical or chemical disruption of these hepatic afferent nerves has been shown to reduce the abundance of colonic peripheral regulatory T (pTreg) cells, which is attributed to decreased expression of aldehyde dehydrogenase (ALDH) and impaired retinoic acid synthesis by intestinal antigen-presenting cells.¹⁴¹ In addition, the Gut-Liver-Brain coordinated regulation involves the formation of the cholinergic anti-inflammatory pathway, sensing of gut- and liver-derived molecules by afferent neuron terminals, modulation via the hypothalamic-pituitary-adrenal (HPA) axis through glucocorticoids, engagement of serotonin receptors, and regulation through immune pathways.¹⁴² In summary, all these organ responses feed back to the neuro-humoral-immune system, while additional signals such as HIF-1, cytokines, lactate, and neurotransmitters serve as biomarkers of sepsis severity and modulate organ function.

On this basis, beyond immune mediators and endocrine signals, neurotransmitters play a critical role in mediating inter-organ communication and regulation during sepsis, modulating immune responses, vascular endothelial function, and the progression of multi-organ injury, thereby offering novel insights into sepsis-associated MODS. Dopamine, a classical central neurotransmitter, has been shown to significantly inhibit the expression of aconitate decarboxylase 1 (ACOD1) induced by bacterial LPS, which is a key immunometabolic regulator, and its overactivation exacerbates inflammatory responses in sepsis.¹⁴³ By suppressing ACOD1, dopamine may mitigate sepsis-associated immune dysregulation and organ injury.¹⁴⁴ Endothelial dysfunction, a central feature of MODS, is also modulated by neurotransmitters such as dopamine, which can regulate vascular tone, microcirculation, and inflammatory mediator release, thereby affecting endothelial permeability and organ perfusion.¹⁴⁵ In addition, the central nervous system communicates with peripheral organs via neuro-immune axes, such as the vagus nerve reflex; imbalances in neurotransmitters like glutamate may induce prolonged neuroinflammation and cognitive dysfunction through NMDA receptor-mediated pathways, worsening MODS.¹⁴⁶ Programmed cell death pathways, including PANoptosis, represent key mechanisms in organ injury,¹⁴⁷ and neurotransmitters may influence these processes via modulation of mitochondrial function (eg, HIF-1 α) or immunometabolic signaling.⁴⁹ Collectively, neurotransmitters contribute to sepsis-induced MODS through immune modulation, endothelial protection, central-peripheral organ communication, and regulation of cell death, providing critical insights into inter-organ crosstalk and potential therapeutic strategies.

From Mechanistic Insights to Translational Challenges in Therapeutic Targeting

MODS induced by sepsis remains a leading cause of clinical mortality, with effective interventions still extremely limited. Various experimental models have revealed the central role of immunometabolic reprogramming in the

development of MODS, while metabolic crosstalk networks between organs serve as key channels amplifying tissue injuries. Although mechanistic studies have advanced considerably, numerous obstacles persist in translating these experimental findings into clinical applications.

Intervention Strategies Remain at the Target Island Stage

Current interventions largely focus on inhibiting single molecules or modulating isolated metabolic pathways, eg suppressing lactate production, restoring mitochondrial function, or regulating macrophage metabolic polarization. However, such strategies often fail to address the highly dynamic and spatiotemporally heterogeneous pathological environment of sepsis. In fact, immunometabolic pathways may exhibit biphasic effects depending on the timing and organ context (eg, early pro-inflammatory responses help pathogen clearance, whereas late-phase activation may induce immunoparalysis). Premature or delayed intervention could therefore worsen the disease.

In the early stage of sepsis, the immune response is highly activated, and cellular metabolism rapidly shifts towards glycolysis to support the rapid proliferation and activation of immune cells. The therapeutic strategy during this phase should focus on controlling excessive inflammation and preventing immune-mediated tissue damage. One such approach is the use of multifunctional nanoparticles that scavenge multiple inflammatory mediators can alleviate cytokine storms, exhibiting both antibacterial effects and the ability to clear various inflammatory mediators, thereby effectively mitigating acute lung injury observed in the CLP model.¹⁴⁸ Similarly, as the M1 polarization of macrophages intensified, it led to ferroptosis and exacerbated the acute lung injury symptoms induced by CLP.¹⁴⁹ When glycolysis in macrophages was inhibited, the secretion of inflammatory cytokines was consequently reduced, demonstrating a protective effect in the LPS model.⁷³ However, premature immunosuppression may suppress effective pathogen clearance, delay optimal treatment, and exacerbate the spread of infection. Diethylhexyl phthalate (DEHP), an environmental immunotoxicant that disrupts the immune system, has been shown to aggravate immunosuppression and organ injury in the CLP model.¹⁵⁰

As sepsis progresses, the immune system enters a state of immune suppression, characterized by a decline in immune cell function and an increased susceptibility to secondary infections. During this phase, metabolic dysregulation often leads to diminished tissue repair and further organ dysfunction. At this point, therapeutic strategies should focus on restoring immune function and promoting metabolic recovery. Research has shown that immune checkpoint inhibitors (such as anti-PD-1 antibodies) can help restore T cell function during the immunosuppressive phase, improving immune responses and enhancing pathogen clearance.¹⁵¹

Moreover, restoring metabolic balance is crucial in the treatment of immune suppression. Some studies suggest that interventions aimed at supplementing NAD⁺, improving mitochondrial function, and activating fatty acid oxidation pathways can reverse immune suppression (Delano and Ward, 2016). For instance, supplementation with NMN (nicotinamide mononucleotide) has been shown in mouse models to restore mitochondrial function, enhance T cell activity, and improve immune responses.^{143,152} Similarly, activation of fatty acid oxidation has been proven to promote immune cell function and reduce organ damage.¹⁵³

Clinically, the effectiveness of sepsis treatment depends not only on the therapeutic interventions themselves but, more critically, on the precise timing of their implementation, as both premature and delayed interventions may exacerbate immune dysregulation and worsen patient outcomes. Substantial evidence indicates that early and appropriate administration of antibiotics remains the cornerstone for improving survival; however, current guidelines are limited in patient stratification and time-sensitive decision-making, highlighting the urgent need to integrate dynamic risk assessment with real-time physiological monitoring to optimize the therapeutic window for antibiotic initiation.¹⁵⁴ With the growing understanding of immune-metabolic reprogramming in sepsis, therapeutic strategies are shifting from single-target interventions toward stage-specific, dynamically adjusted multimodal approaches. During the initial phase of the disease, interventions primarily target the limitation of excessive inflammation to prevent immune dysregulation, while in the later phase, they aim to reestablish immune competence and metabolic homeostasis, facilitating tissue repair and the restoration of organ function.¹⁵⁵ In this context, although corticosteroids are widely used, effectiveness is not uniform across patients. Treatment outcomes can be affected by individual factors, such as relative adrenal insufficiency (RAI), and prolonged administration may result in immunosuppression and metabolic disturbances.^{156,157} Antibiotics play a pivotal role in sepsis management by controlling infection and reducing mortality, yet antibiotic administration is

associated with challenges such as overuse, antimicrobial resistance, and adverse effects.^{158,159} Consequently, growing interest has emerged in exploring additional therapeutic approaches. Selenium and its organic form, selenomethionine, demonstrate potential immunometabolic protective effects through modulation of oxidative stress, mitochondrial function, and inflammatory responses.^{160,161} Mesenchymal stem cells and derived extracellular vesicles have been shown to alleviate immune dysregulation and improve outcomes in animal models; however, clinical translation remains limited by challenges related to standardization and safety.¹⁶² Notably, nanotechnology provides novel platforms for the targeted delivery of trace elements, bioactive molecules, and cell-derived therapeutics, with the potential to achieve more efficient and low-toxicity precision interventions.¹⁶³ Current research trends emphasize personalized treatment guided by clinical phenotyping and real-time immunometabolic monitoring, with a focus on the systemic regulatory roles of key immunometabolic nodal proteins, including mTOR, HIF-1 α , and the SIRT family, in inter-organ crosstalk.¹⁶⁴ Overall, future sepsis management should build upon early anti-infective therapy by integrating time-resolved metabolic monitoring, targeted immunometabolic modulation, and advanced delivery technologies, thereby facilitating the clinical translation of multimodal, stage-specific intervention strategies.

The Significant Gap Between Animal Models and Clinical Practice

Although existing experimental models simulate human infectious sepsis with considerable physiological similarity, they cannot fully replicate the complexity of human sepsis. The stability and individual variability of CLP model, including the number of perforations or degree of fecal leakage, significantly influence inflammatory severity. Although the current experimental protocols are highly detailed, variations in body weight and species of experimental animals result in inevitable discrepancies in the exact location of cecal ligation and puncture. Moreover, in the experimental process, excessive force applied during extrusion of intestinal contents, as well as anatomical variations in the vasculature on the cecal surface, may lead to stage-specific differences. The LPS model allows precise control over the magnitude of systemic inflammation, yet it fails to capture the dynamic complexity of host-pathogen interactions, microbial translocation, and progressive infection. Pathogen-specific bacteremia model can be employed to investigate the effects of defined microorganisms; however, it may overlook the interplay among multiple microbial species. Immune metabolic features differ markedly between rodents and humans, including T cell subset proportions and macrophage polarization lineages.¹⁶⁴ Therefore, for studies on immune responses and inflammatory diseases, at least those related to sepsis, both human and experimental animal data should be considered. Most studies overlook common comorbidities (eg, diabetes, obesity, aging), which are prevalent in clinical settings, male young adult rats are generally selected, which reduces variability but overlooks the confounding effects of these clinically prevalent conditions. Differences in endpoints further complicate translation. Animal experiments usually focus on survival or tissue inflammation, while clinical practice emphasizes organ support duration, biomarker dynamics, and functional recovery. Hence, it is urgent to develop more translationally relevant humanized models, organoid systems, and large animal models that mimic clinical scenarios, as well as to encourage incorporation of individual heterogeneity and temporal analyses in animal experiments. However, each prospective direction faces its own challenges. Humanized mice are xenotransplantation models in which a functional human immune system is established through the expansion of engrafted human cells.¹⁶⁵ It has been demonstrated that humanized mice experience more severe weight loss within 5 days after CLP induction, thereby validating the translational relevance, given that cachexia is a recognized clinical manifestation of sepsis. In contrast to wild-type counterparts, the emergence of T-cell anergy and Fas expression constitutes a human-specific response to septic challenge.¹¹⁰ The key applications of humanized mouse models have focused on elucidating the mechanisms of apoptosis, the interactions of staphylococcal superantigens with the immune system, the development of vasculitis in hemorrhagic fever and meningitis, and the short- and long-term epigenetic reprogramming of leukocytes.¹⁶⁶ However, further limitations to the use of humanized mice in sepsis research are their substantial cost and restricted availability. These models are costly to acquire and maintain, and the reconstitution of a functional immune system after stem cell engraftment typically requires several weeks.

Integrative Multi-Omics Analysis of Key Biomarkers and Systemic Mechanisms in Sepsis

Beyond lactate, a key biomarker in sepsis, preclinical studies have identified multiple additional signals and factors worthy of investigation. Lactate-associated proteins, including monocarboxylate transporters (MCT1, MCT4) and the receptor GPR81, play critical roles in regulating immune cell function and may serve as complementary biomarkers.¹⁶⁷ Lactylation, a post-translational modification, has been implicated in sepsis-induced myocardial depression, suggesting that enzymes and metabolites within the lactate metabolic pathway may hold biomarker potential.¹⁶⁸ Epigenetic regulators, such as lactate-mediated m6A RNA modifications, contribute to sepsis-associated acute lung injury and may represent novel research targets.¹⁶⁹ Immunometabolic molecules, including the lactate-ROS axis and the sphingosine-1-phosphate (S1P) signaling pathway, reflect early hyperinflammatory responses and impaired macrophage anti-bacterial function, respectively, and could serve as early warning signals.¹⁷⁰ Vascular endothelial injury markers, such as glycocalyx components, may additionally indicate microvascular dysfunction in sepsis.^{58,171}

Advances in rapid detection technologies have further enhanced the utility of biomarkers. Near-infrared fluorescence (NIRF) lactate assays and electrochemical sensing platforms enable faster bedside monitoring compared with conventional methods.^{172,173} Integrative multi-omics analyses, encompassing transcriptomics, metabolomics, proteomics, single-cell omics, and extracellular vesicle profiling, improve diagnostic specificity while providing a comprehensive view of immunometabolic regulation, organ injury, pharmacological mechanisms, and potential therapeutic targets in sepsis.^{174,175} Systemic network mapping across multiple organs and cell types facilitates understanding of inter-organ crosstalk mechanisms, such as the liver–heart and lung–gut axes, and enables identification of key regulatory nodes and metabolic switches, including NAD⁺ metabolism, ubiquitination, and the tryptophan-kynurenine pathway. Time-resolved dynamic atlases, combined with pseudotime analysis and dynamic metabolic flux simulations, reveal the sequential progression of pathological events.¹⁷⁶ Furthermore, artificial intelligence and machine learning tools can integrate these complex omics datasets to construct biomarker panels predictive of disease progression and therapeutic response, laying a foundation for precision medicine.¹⁷⁷

Overall, integrating multi-mechanism biomarkers with high-throughput multi-omics analyses, rapid detection technologies, and AI-driven analytical tools holds promise for enabling early warning, dynamic monitoring, and precision intervention in sepsis, thereby facilitating the translation of preclinical findings into clinical applications.

In vivo Biosensors Enable Real-Time Dynamic Monitoring of Sepsis Metabolic States

Traditional sepsis monitoring relies on static measurements, such as intermittent blood gas analysis, lactate, PCT, and C-reactive protein (CRP), which inadequately capture the rapidly fluctuating metabolic and immune response dynamics. Recently, implantable or wearable biosensors have emerged that enable continuous real-time monitoring of parameters including lactate, glucose, pH, and inflammatory mediators, which has been an innovative direction. Coupled with artificial intelligence, these technologies hold promise for novel approaches to assess disease evolution and guide personalized interventions.^{178,179} Moreover, non-invasive biosensors for small animals remain in early development stages and urgently require further advancement. The sensors could capture key signals, such as IL-3,¹⁸⁰ IL-6, IL-8, IL-10, IP-10, TNF-related apoptosis-inducing ligand, d-dimer, CRP, and granulocyte colony-stimulating factor,¹⁸¹ exhibiting excellent specificity and sensitivity. In experimental animal models, a paper-based biosensor for the detection of sepsis in the FIP mouse model has been shown to detect an immediate increase in matrix metalloproteinase-9 levels within 1 hour, although blood samples still need to be extracted.¹⁸² However, currently available biosensors for rodents remains mostly invasive, such as implantable sensors monitoring temperature or electrocardiography.^{177,178} The devices require surgical implantation and a relatively long recovery period, and expensive. Non-invasive sensors for small animals, similar to wearable human devices that monitor heart rate or blood pressure as auxiliary medical devices, are still in the preliminary stage and remain to be developed.

Summary and Outlook

Sepsis-induced MODS is a complex and challenging pathological process in clinical practice. In recent years, immune metabolic reprogramming has been increasingly recognized as a central mechanism in sepsis and associated organ injuries. Inter-organ crosstalk through metabolic products, inflammatory mediators, and immune signals to form a complex crosstalk network, jointly participating in the onset and progression of MODS. Although animal models and multi-omics technologies have greatly enriched our understanding of the immune metabolic mechanisms in sepsis, significant challenges remain in translating these basic research findings into clinical applications, including pathological heterogeneity, model limitations, and the lack of precise temporal intervention. Researchers can try to overcome the limitations by integrating systems biology and dynamic metabolic monitoring to reveal immune metabolic networks across spatial and temporal dimensions and to identify key regulatory nodes across organs in the future. The application of innovative in vivo biosensors and artificial intelligence technologies will open new avenues for real-time monitoring of metabolic states in sepsis, precise disease assessment, and personalized treatment. Moreover, the development of more clinically relevant humanized models and diverse animal models is also crucial.

Overall, precise intervention in immune metabolism and inter-organ crosstalk, combined with multidisciplinary technologies, holds promise as an effective strategy to improve sepsis outcomes and reduce mortality. With the continuous deepening of our understanding of immune metabolic networks in sepsis, the prospects for translational medicine are encouraging.

Generative AI Statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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