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REVIEW ARTICLE

# Bacterial infection and sepsis-associated inflammation: Mechanistic insights and emerging clinical perspectives

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## Abstract

Sepsis is typically initiated by bacterial infection and the associated immune dysregulation displays a complex, dynamic biphasic immune response characterized by hyperinflammation followed by immunosuppression. In the initial period, pathogens activate the innate immune system through receptors such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), resulting in the massive release of cytokines, including IL-1β, IL-6, and IFN-γ, thereby initiating a "cytokine storm" that leads to vascular endothelial damage, complement activation, and the induction of abnormal cellular aggregation. Sustained activation of inflammatory signals initiates inflammasome-mediated cell death, including pyroptosis-apoptosis-necroptosis (PANoptosis), leading to systemic inflammation and organ dysfunction. Later, the host develops an immunosuppressive phase characterized by increased anti-inflammatory mediators (e.g., IL-10 and TGF-β), exhaustion of B, T, and NK cells, and immune checkpoint-mediated immune paralysis. The stepwise progression of these two stages suggests that sepsis is not simply a consequence of uncontrolled inflammation but rather reflects immune system reprogramming. A better understanding of the molecular basis of inflammation and immunosuppression, particularly the crosstalk among cell death pathways, metabolic reprogramming, and immune regulation, may facilitate timely precision interventions and the restoration of host immune homeostasis in sepsis.

**Keywords:** Sepsis, Bacterial infection, Cytokine storm, Immune dysregulation, Inflammatory cell death, Metabolic reprogramming, Immune checkpoints, Precision immunotherapy

## 1 INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, and its pathogenesis is generally considered a highly complex process involving pathogen invasion and host immune dysregulation [1]. As one of the most common pathological conditions in intensive care practice, this life-threatening condition is a major cause of infection-related death and is characterized by remarkable heterogeneity and clinical complexity driven by immune and metabolic dysfunction. Technological advances in multi-omics have now shown that sepsis is fundamentally a multidimensional disease mediated by interconnected immune, metabolic, and inflammatory networks and cannot be fully explained by traditional inflammatory paradigms [2].

Bacterial infections are the most common cause of sepsis. Pathogens stimulate the host's innate immune responses via



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various pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and NOD-like receptors (NLRs), resulting in a cascade of cytokine production and activation of inflammatory signaling. It is this transition from beneficial inflammation to the detrimental cytokine storm that underpins the high mortality of sepsis. Epigenetic regulators, such as peptidyl arginine deiminase 4 (PADI4), and metabolic reprogramming, such as enhanced glycolysis, contribute to inflammasome activation, immune cell exhaustion, and macrophage polarization, thereby reshaping multilayered immune regulatory networks [3]. Pathogens have varying strategies to evade immune responses. For instance, Neisseria meningitidis sustains bacteremia by pilus-dependent adherence to the endothelium lining blood vessels, Group B Streptococcus can compromise the integrity of the neonatal blood-brain barrier leading to neuroinflammation, and Klebsiella pneumoniae uses a coordinated network of virulence factors that co-opt antibiotic resistance mechanisms to facilitate dissemination throughout the body [4-6]. These differences demonstrate that bacterial infections are multidimensional in the pathological development of sepsis.

The inflammatory response is also influenced by host factors that determine both the range and severity of the response. The high incidence of sepsis in the elderly population is biologically associated with increased inflammation via the immunometabolic axis related to aging, metabolic disorders, and gut microbiota dysbiosis. The biphasic immune response underpins the pathophysiology of sepsis: an early phase dominated by hyperactivated innate immune responses and cytokine storm, followed by a later phase of profound immunosuppression and T cell exhaustion—resulting in dynamic dysregulation characterized by "hyperinflammation and immune paralysis". Transcriptomic profiling has enabled the identification of sepsis molecular subtypes, including Sepsis Response Signature 1 (SRS1; immunosuppressive) and SRS2 (proinflammatory/activated), thereby providing a conceptual framework for patient stratification and potential personalized therapeutic strategies [7]. Meanwhile, metabolic reprogramming has been identified as an important driver of immune hyporesponsiveness. Excessive glycolysis and impeded oxidative phosphorylation not only weaken the efficacy of immune cells but also aggravate metabolic dysregulation and organ damage, thus magnifying immunosuppression.

Furthermore, comprehensive systems-level modeling of these pathophysiological networks is advancing sepsis research beyond a single inflammatory paradigm. Many signal transduction pathways, such as NF-κB, MAPK, and JAK/STAT, converge in different tissues giving rise to complex inflammatory networks. Conversely, immune suppression and tissue repair in the late phase of inflammation are induced by negative feedback loops such as autophagy, the nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant pathway, and thymic stromal lymphopoietin (TSLP), which may reflect this shifting balance between host defense and restoration of homeostasis [8]. The diagnostic paradigm of sepsis is evolving across evidence, clinical trials, and definitions. Clinical research is even changing the model of diagnosis for sepsis, shifting from traditional symptom-based scoring systems toward molecular multi-omics–based diagnostic frameworks. The simultaneous assessment of biomarkers and metabolic markers has substantially improved the sensitivity of early diagnosis, while host genetic polymorphisms have offered a genetic basis for individual susceptibility. Immunophenotypes and metabolism-based precision stratification approaches are paving the way for the concept of personalized immune reconstruction as a potentially curative therapeutic strategy.

Sepsis is not a random consequence of repeated immune activation but rather reflects systemic breakdown under persistent infectious challenge. Bacterial infection disrupts the balance between immune and metabolic processes, driving metabolic reprogramming of immune cells and subsequent immune dysfunction. For example, sepsis can induce persistent activation of $CD4^+$ T cells accompanied by non-specific IL-17 production, a process associated with mitochondrial dysfunction and enhanced glycolysis that may persist long after the initial infection and impair host responses to secondary challenges [9]. These alterations ultimately drive the host into a state of systemic instability that extends beyond localized inflammation and progresses toward systemic physiological reorganization.

Advances in multi-omics technologies and systems biology have further reshaped the understanding of sepsis pathogenesis. Evidence indicates widespread alterations in immune and metabolic signaling pathways in septic patients, with several pathways correlating with immune cell abundance and patient survival [10]. These system-level perturbations highlight that sepsis is not merely an exaggerated inflammatory response but a complex immune-metabolic dysregulation involving multilayered regulatory networks. Because this dysregulation originates from host responses to invading pathogens, understanding the molecular mechanisms of bacterial infection is essential for elucidating how localized infection progresses to systemic sepsis.

## 2 MECHANISMS OF BACTERIAL INFECTION AND THE PROGRESSION OF SEPSIS

### 2.1 Bacterial invasion and host response

The initiation of sepsis is a classical example of pathogenic attack and host response imbalance. In this process, bacterial invasion activates PRR-mediated inflammatory cascades. This host defense immune response directed against pathogen elimination is exaggerated and becomes self-amplifying, particu-

larly within cytokine signaling networks in a process known as a "cytokine storm". Such an overwhelming response is thought to stimulate the release of numerous cytokines, leading to microcirculatory dysfunction and eventually multiple organ failure [11]. In recent years, system-wide proteome studies have also identified that dysregulated activation of the complement and coagulation cascades, together with metabolic reprogramming, constitutes key molecular networks responsible for septic liver injury. These molecular imbalances are functionally related and ultimately contribute to immune and organ dysregulation [12].

The delicate structure and precise regulation of immune responses have become more clearly delineated in recent years. Loss of the epigenetic regulators PADI2 or PADI4 suppresses NLRP3 inflammasome activation and promotes M2 macrophage polarization, thereby reducing tissue inflammatory injury [3]. This discovery not only demonstrates the importance of epigenetic changes in the course and outcome of sepsis but also indicates that modulating immune cell fate may provide a new therapeutic avenue for this disease. Clinically, the Liverpool quick Sequential Organ Failure Assessment (LqSOFA) instrument correlates with downstream parameters of immune and circulatory dysregulation by providing a scoring system that represents the degree of organ dysfunction [13]. Various pathogens further aggravate immune dysregulation through distinct mechanisms. N. meningitidis sustains bacteremia by dynamic retraction of type IV pili, which themselves drive a positive feedback loop between inflammation and the coagulation cascade [4]. In contrast, Group B Streptococcus itself can bypass the neonatal blood-brain barrier and cause neuroinflammation and white matter damage. Importantly, this pathological course is independent of hypoxic pathways, emphasizing the infection-mediated neuropathological phenotype that is characteristic of bacterial sepsis [5]. In fetal sepsis, organisms traverse the placenta and are distributed to a number of organs, indicating a twofold mechanism of "direct pathogen invasion combined with dysregulatory host immune factors" [14].

Increasing attention has been paid to the role of gut-derived pathogens in sepsis. Klebsiella pneumoniae can cause systemic infection through translocation from the intestinal compartment, facilitated by $pks^+$ virulence traits and antibiotic resistance that undermine host barriers and promote organ colonization [6]. On the other hand, age-related remodeling of the gut microbiota substantially promotes pathogen immune evasion, leading to exaggerated inflammatory responses and organ injury, which may provide a biological interpretation for the increased susceptibility of elderly individuals [15]. Metabolic conditions also profoundly influence the course of inflammation. Immune cells can be activated under hyperglycemic conditions, promoting glycolytic pathways and aggravating inflammation and lactic acidosis; moderate glucose restriction contributes to metabolic homeostasis via gluconeogenesis, thereby mitigating inflammation and organ injury [16]. Furthermore, some pathogen surface proteins, such as GPAC, can rapidly trigger neutrophils to secrete vasoactive products and TNF-α, thereby escalating the pathological inflammatory response [17]. Other environmental conditions, such as prolonged alcohol exposure, also enhance systemic and gut inflammatory responses by compromising intestinal barrier function with concomitant increased release of Th1/Th17 cytokines [18].

These endogenous host pathways are also important mechanisms for immunological dysregulation. Skeletal muscle Myeloid differentiation primary response 88 (Myd88) signaling regulates sex-specific cytokine release and neutrophil recruitment, with consequences for sepsis survival [19]. Importantly, recent investigations have indicated that modulating the host in addition to targeting pathogens may provide new treatments for sepsis. For example, CYP1A1 has been identified as a negative regulator of host anti-infective responses. Its small-molecule inhibitors may modulate macrophage phagocytic function and exert therapeutic effects against multidrug-resistant bacterial infection [20]. This finding suggests a potential therapeutic strategy for future interventions: reshaping immune and metabolic networks, interrupting the vicious circle of inflammation and organ damage, and offering novel ways for precision medicine interventions in sepsis. While bacterial invasion and systemic dissemination define the pathological onset of sepsis, the pivotal transition occurs at the molecular interface where pathogen-associated signals are sensed and translated into immune activation. This shift from invasion to recognition marks the progression from localized infection to systemic inflammatory dysregulation. Consistently, the mature regulatory dendritic cell program is induced within ~24 h after septic challenge through TNFRSF–NF-κB and IFNGR2–JAK–STAT3 signaling. Analysis of publicly available single-cell datasets from patients with COVID-19 further confirmed the presence of mregDC populations in human sepsis-associated immune responses, underscoring the importance of pathogen sensing and downstream immune activation in shaping septic inflammation [21].

### 2.2 Pathogen recognition and immune activation

Pathogen recognition and subsequent immune activation are central in the initiation and progression of sepsis. Molecular sensors in both host and microbial compartments, including PRRs and inflammasomes, recognize pathogen-associated invasion signals and initiate early host defense responses. However, this mechanism may be dysregulated and progress into destructive inflammation during sepsis, further leading to organ damage and immune failure.

At the innate immunity level, neutrophils and erythrocytes have a much broader function than was previously believed. The Sema7A-PlexinC1 signaling axis promotes adhesion, neutrophil chemotaxis, and platelet aggregation to enhance the pulmonary inflammatory response; Erythrocytes not only rec-

ognize microbial DNA via TLR9 but also trigger macrophage activation and inflammatory cytokine release, revealing a previously unrecognized role of erythrocytes in pathogen detection [22, 23]. Meanwhile, the NLRP6 inflammasome induces overwhelming inflammation via IL-18 and impairs T cell survival, facilitating host immune dysfunction and collapse [24]. The simultaneous release of bacterial outer membrane vesicles and ATP can locally suppress neutrophil function, mediate degranulation, and disrupt systemic inflammatory balance, generating a "double-edged sword" mechanism between pathogen and host responses [25, 26].

Pathogen-derived immune-evasion strategies further aggravate host immune dysregulation. Streptococcus pneumoniae BgaA promotes adhesion and resistance to bacterial killing, thereby activating coagulation pathways and aggravating tissue damage, which further intensifies inflammatory pathology; Klebsiella pneumoniae is antibiotic resistant, and thus successfully evades immune clearance and perpetuates the inflammation-damage cycle; Group B Streptococcus enhances biofilm formation and invasion with the aid of its LytSR system by interfering with host immune recognition [27-29]. Together, these pathogen-specific mechanisms contribute to immunological dysregulation during sepsis.

At the level of the immunological network, sepsis is characterized by reduced adaptive immune activation together with excessive innate immune activation. Consistent with the therapeutic relevance of infection-driven immune dysregulation, IOX1 has been shown to regulate endotoxemia and bacterial sepsis caused by Escherichia coli and carbapenem-resistant Acinetobacter baumannii, while suppressing multidrug-resistant bacterial growth through inhibition of DNA gyrase [30]. In parallel, postoperative sepsis further exemplifies immune suppression within this dysregulated network, as persistent CTCF binding to the major histocompatibility complex (MHC)-II region prevents the expression of CIITA and human leukocyte antigen (HLA)-II genes, thereby directly impairing antigen-presenting function and worsening immune paralysis [31].

Of note, host and bacterial metabolites are involved in regulating the magnitude of inflammation. Vascular endothelial growth factor (VEGF) enhances the phagocytic and lysosomal functions of endothelial cells through cyclic adenosine monophosphate–transcription factor EB signaling, thereby promoting the elimination of intracellular Streptococcus pyogenes; by contrast, VEGF-depleted vessels show impaired bactericidal activity and support bacterial dissemination [32]. The gut-derived metabolite indole-3-lactic acid targets PFKFB2 to suppress glycolytic flux and reduce cytokine storm severity and organ injury [33]. Concurrently, DJ-1 deletion induces autophagolysosome formation, and enhances bacterial clearance and immune response [34]. These findings demonstrate the importance of "immune-metabolic coupling" in controlling inflammation during sepsis. In addition, some endogenous molecules show promise in protecting against inflammation. Rhamnose inhibits TLR4/ROS-mediated caspase-1 activation and diminishes IL-1β/IL-18 release, attenuating pyroptosis and oxidative injury caused by resistant bacteria; DLL1, as a ligand for monocytes, specifically boosts inflammatory signaling in infection by enabling the immune response to discriminate infectious from non-infectious inflammation [35, 36]. Although complement is acutely activated in early sepsis, its function becomes decoupled from disease progression and patient outcome, and it may play a role more as an early pathologic trigger than as a driving force in later stages [37].

These findings indicate that pathogen recognition and immune activation in sepsis constitute a complex and dynamically dysregulated network involving classical PRR and inflammasome signaling, pathogen immune-evasion strategies, and host immunometabolic crosstalk. This framework not only deepens our understanding of sepsis immune pathology but also highlights potential strategies for precision diagnosis and therapy by restoring the balance between host defense and inflammatory injury.

Within this network, inflammatory signaling pathways interact across multiple molecular signals to reinforce the inflammatory response, driving the transition from localized immune responses to systemic inflammatory dysregulation. Cytokines play pivotal roles in this process, exerting dual effects in sepsis: excessive activation can trigger a "cytokine storm", whereas persistent dysregulation may lead to immunosuppression [38]. The extensive cross-activation among these pathways forms a highly interconnected inflammatory regulatory network (**Table 1**) and ultimately converges on the molecular drivers of inflammatory storms. Although pathogen recognition initially serves as a protective response, sustained amplification of these signaling networks promotes the release of cytotoxic mediators and bacterial toxins, which directly damage cellular structures and organelles. This transition from immune activation to toxin-mediated cellular injury represents a critical step in the progression of sepsis pathogenesis.

### 2.3 Bacterial toxins and host cell damage

Bacterial toxins and host response dysregulation induce cellular injury and organ failure. Several signaling pathways and organelle injury processes have been implicated in sepsis, indicating that they are not only part of the pathological mechanism but also potential therapeutic targets.

In skeletal muscle, SPSB1 worsens sepsis-induced muscle atrophy and regeneration failure through inactivation of the TβRI–Akt–myogenin signaling pathway and suppression of protein synthesis [69]. Intestinal ACE2 can modulate the gut microbiota and the metabolite 5-MTP, activate the PI3K–AKT–WEE1 pathway, and support barrier function, thereby mitigating sepsis and multi-organ damage [70]. In the myocardium, actin/

**Table 1. Roles of inflammatory cytokine networks and signaling pathways in cytokine storms**

| Inflammatory/ regulatory factors | Upstream triggering mechanisms | Major signaling pathways | Downstream effects | Clinical significance | References |
|---|---|---|---|---|---|
| miR-30d-5p | TNF-α stimulates polymorphonuclear neutrophils to release exosomes | Upregulates NLRP3 inflammasome via the NF-κB signaling pathway | Induces M1 polarization and pyroptosis in macrophages | Potential novel therapeutic target for sepsis-associated ALI | [39] |
| IL-1β | Polymicrobial sepsis induced by cecal ligation and puncture (CLP) | Activates NF-κB and autophagy via the NLRP3/IL-1β pathway | Leads to cardiomyocyte atrophy and impaired systolic and diastolic function | Inhibition of NLRP3/IL-1β may prevent sepsis-induced cardiomyopathy | [40] |
| IL-6 | Sepsis induced by CLP | Cortical TGF-β1/Smad3 and medullary IL-6/STAT3 signaling pathways | Mitigates renal epithelial-mesenchymal transition, apoptosis, and inflammation | PRMT1 may serve as a novel therapeutic target for sepsis-induced kidney injury | [41] |
| IL-8 | Sepsis-induced neuroinflammation | Cytokine–receptor interactions and IL-17 signaling pathway | Leads to delirium, coma, and other neurological dysfunctions | IL-8 may serve as a diagnostic marker and therapeutic target | [42] |
| IL-10 | Excessive inflammation induced by LPS or sepsis | IL-10–mediated anti-inflammatory response | Suppresses pro-inflammatory cytokine production and improves survival | $CD169^+$ macrophages may serve as a novel target for anti-inflammatory therapy | [43] |
| IFN-γ | Macrophages stimulated with LPS combined with IFN-γ | Inhibits PINK1-mediated mitophagy via STAT1-dependent pathway | Promotes macrophage activation and bacterial clearance | Mitophagy inhibition may improve sepsis outcomes | [44] |
| MCP-1 | Polymorphism of MCP-1 gene rs1024611 G allele | Upregulation of MCP-1 expression promotes inflammatory responses | Increased pro-inflammatory cytokines; susceptibility to sepsis in diabetes | MCP-1 polymorphism may serve as a risk marker for diabetic sepsis | [45] |
| HMGB1 | Sepsis-induced hyperlactatemia | HMGB1 modifications mediated by GPR81/Hippo/YAP and p300/CBP | Lactylation/acetylation of HMGB1 and its release via exosomes | Targeting lactate/GPR81 signaling may improve sepsis outcomes | [46] |
| IL-12 | Sepsis induced by LPS or CLP | Heat shock protein 40-like protein 1 (HLJ1)/IL-12/IFN-γ axis | Enhanced IFN-γ production by NK cells leads to hyperinflammation and mortality | Targeting HLJ1 may provide therapeutic intervention for IL-12/IFN-γ axis–mediated sepsis | [47] |
| IL-18, NLRP3 | Sepsis-associated acute kidney injury (SA-AKI) | Activation of the NLRP3 inflammasome pathway | Promotes inflammatory responses, leading to renal dysfunction | Potential diagnostic biomarker for SA-AKI | [48] |
| IL-17 | Sepsis-induced pancreatic injury via CLP | RhoA/ROCK and STAT3/RORγt signaling pathways | Suppresses Th17 differentiation and pancreatic cell apoptosis | Combination of Fasudil with SR1001 may exert synergistic therapeutic effects in sepsis | [49] |
| TGF-β | Sepsis- or LPS-induced inflammatory response | Regulates glycolysis via the TGF-β/mTOR/c-MYC signaling pathway | Enhances glycolysis while suppressing pro-inflammatory cytokines, promoting coagulation | TGF-β may serve as a therapeutic target in sepsis | [50] |
| IL-4, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) | Activation of B and T cell Nociceptin/Orphanin FQ receptor (NOP) system induced by LPS/PepG stimulation | N/OFQ-NOP autocrine signaling pathway | Inhibits cell migration and reduces GM-CSF release | NOP antagonists may serve as potential therapeutic agents for sepsis | [51] |
| Aquaporin-3 (AQP3), IL-33 | Upregulation of AQP3 expression due to CC genotype | High AQP3 expression is associated with elevated IL-33 levels | Significantly reduced 30-day survival in patients | AQP3 polymorphism may serve as a prognostic marker | [52] |
| C5a | Excessive complement C5a production in sepsis | Activation of MAPK/AKT kinase pathways via C5aR | Induces apoptosis of adrenal medulla cells and dysregulation of inflammatory proteins | C5a inhibition may protect adrenal function and improve sepsis outcomes | [53] |

| | | | | | |
|---|---|---|---|---|---|
| Plasminogen activator inhibitor-1 (PAI-1) | 4G/5G polymorphism of the PAI-1 gene | Elevated PAI-1 levels affect neutrophil activity | Altered neutrophil activation and increased mortality | Modulating PAI-1 may improve sepsis outcomes | [54] |
| Ang-2, VEGF-A | Sepsis-induced vascular barrier disruption | Dual targeting of Ang-2/VEGF-A | Reduces inflammatory cell migration and cytokine release | A2V bispecific antibody may serve as a novel therapeutic agent for restoring vascular barrier in sepsis | [55] |
| S100A8/A9 | High levels of S100A8/A9 released by PMNs in sepsis | S100A8/A9–Nrf1–mitochondrial complex I–ZBP1 signaling pathway | Induces mitochondrial dysfunction and endothelial cell PANoptosis | S100A8/A9-high neutrophils may serve as prognostic markers and therapeutic targets | [56] |
| MIP-1α | LPS-induced sepsis model | Regulates the RAAS pathway and nitric oxide levels | Attenuates pulmonary and renal inflammation and tissue injury | Dexamethasone may serve as a potential therapeutic strategy for sepsis | [57] |
| RANTES | Immune dysregulation triggers a pro-inflammatory milieu | Monocyte-mediated pro-inflammatory cytokine network | Elevated pro-/anti-inflammatory ratio distinguishes sepsis | Serves as a potential diagnostic biomarker to differentiate sepsis from malaria | [58] |
| IL-22 | CLP-induced sepsis and lung injury | IL-22 activates the STAT3 signaling pathway | Inhibits pulmonary epithelial apoptosis and alleviates inflammation | IL-22 may represent a novel therapeutic strategy for sepsis-induced lung injury | [59] |
| IL-27, IL-27Rα | Neonatal sepsis induces elevated IL-27 expression | IL-27 signaling regulates inflammatory responses | Suppresses excessive inflammation and enhances bacterial clearance | IL-27 antagonism may serve as a novel therapeutic strategy for neonatal sepsis | [60] |
| IL-35 | LPS induces inflammatory activation of endothelial cells | IL-35 activates the STAT1/STAT4 signaling pathway | Inhibits apoptosis and the expression of inflammatory mediators | IL-35 may serve as a potential endothelial-protective strategy in sepsis | [61] |
| IL-37 | Sepsis-induced inflammatory response in lung injury | Mediates apoptosis through the TGF-β/Smad3 signaling pathway | Attenuates pulmonary edema, inflammation, and apoptosis | IL-37 may represent a potential therapeutic target for sepsis-induced lung injury | [62] |
| IL-38 | LPS induces IL-38 expression in macrophages | The IL-38/IL-36R axis regulates macrophage polarization | Inhibits apoptosis and NLRP3 inflammasome activation | IL-38 may serve as a novel immunoregulatory therapeutic target in sepsis | [63] |
| sTREM-1, sST2 | Sepsis-induced activation of immune responses | Inflammatory pathways correlated with SOFA scores | Enhance diagnostic accuracy and prognostic assessment in sepsis | Combined detection may represent a novel diagnostic strategy for sepsis | [64] |
| IL-23 | Sepsis induces excessive inflammatory responses | Activation of IL-23–related inflammatory pathways | Elevated pro-inflammatory levels associated with increased mortality | May serve as an independent biomarker for sepsis diagnosis and prognosis | [65] |
| AKK, RKH, TLR4 | Sepsis reduces intestinal abundance of AKK | RKH directly antagonizes the TLR4 signaling pathway | Suppresses excessive inflammation and mitigates organ injury | AKK or RKH may represent potential therapeutic strategies for sepsis | [66] |
| Sphingosine kinase 1 (SphK1), Sphingosine-1-phosphate (S1P), S1PR1 | Acute ethanol intoxication aggravates sepsis-induced lung injury | Activation of the SphK1/S1P/S1PR1 signaling pathway | Increases vascular permeability, inflammation, and apoptosis | Inhibition of SphK1 may represent a potential therapeutic strategy | [67] |
| GSDMD | S100A8/A9 activates platelet TLR4 during sepsis | S100A8/A9–TLR4–GSDMD pyroptosis pathway | Triggers platelet pyroptosis, promotes NET formation, and amplifies inflammatory cascades | Inhibition of the S100A8/A9–TLR4 axis may represent a novel therapeutic strategy for sepsis | [68] |

myosin degradation by calpain-1 plays a major role in sepsis-induced heart injury. Interventions targeting calcium signaling can mitigate cardiac dysfunction and increase the survival rate [71]. Extracellular histones are also detrimental to the heart, as they cause imbalances in calcium homeostasis and mitochondrial function, resulting in cardiac failure. Inhibition of histones is a novel therapeutic strategy [72].

The impairment of both endothelial and barrier function of vasculature is especially important in the development of sepsis. Sepsis-induced disseminated intravascular coagulation disrupts EXT1/FGFR1-mediated glycocalyx remodeling and enhances barrier damage and pulmonary edema; TGF-β1 derived from platelets induces neutrophil recruitment and promotes extracellular trap formation, leading to thrombosis as well as organ injury [73]. Its absence increases survival, and makes it a candidate therapeutic target [74]. At a later stage after shock, the Angiopoietin-2 (Ang-2)/Tie2 pathway is involved in vascular leakage, and subsequently contributes to remote, indirect Acute Respiratory Distress Syndrome (ARDS).

Inhibition of Ang-2 could restore barrier function and increase survival rate [75]. Additional studies demonstrate that Ang-2 also induces lung injury and increases inflammation by modulating endothelial-neutrophil interactions [76].

Mitochondrial injury and dysfunction are key elements of sepsis-induced organ failure. Mitochondria-related hub genes have been shown to influence energy metabolism and immune microenvironment regulation, which are significantly involved in the pathogenesis and progression of Sepsis-ACM [77]. Histone Deacetylase (HDAC) 3 inhibits mitochondrial quality control by the FOXO1–Rho-associated coiled-coil containing protein kinase (ROCK) 1 axis, driving progression of acute lung injury (ALI); thus, HDAC3 inhibition might represent a promising novel therapeutic opportunity [78]. The mechanosensitive ion channel Piezo1 is triggered during sepsis to induce calcium influx and mitochondrial impairment which in turn disrupts the tight junctions of the intestinal epithelial cells, followed by cellular apoptosis, thereby propagating barrier damage [79].

Immune and reparative functions are also suppressed in the long term. Sepsis may lead to the dysfunction of bone marrow (BM) mesenchymal stem cells (MSCs), which is characterized by mitochondrial depolarization and decreased cytokine expression, thereby disrupting BM homeostasis and long-term immune reconstitution [80]. Recurrent sepsis worsens $CD4^+$ T cell exhaustion, interferes with antiviral immunity, and is consequently associated with long-term mortality, demonstrating the sustained immune consequences of sepsis [81]. Furthermore, artesunate and metabolism-related proteins also show therapeutic potential by regulating hepatic endothelial cell subpopulation proportions, inhibiting inflammatory cytokine release in liver macrophages, and decreasing lymphocyte apoptosis, thereby alleviating liver injury and immune imbalance and supporting their potential clinical application [82]. VDBP is reduced with sepsis and correlated with liver injury and mortality. Its overexpression could protect against oxidative stress and hepatocyte injury, which may have a protective role [83].

Interactions between bacteria-derived molecules and host response mediators constitute central driving forces in the pathogenesis of sepsis. Emerging evidence highlights the critical role of inflammatory cytokine networks in this process. For example, the combined action of tumor necrosis factor with IL-18, IFN-γ, or IL-1β is sufficient to reproduce sepsis-associated tissue injury, indicating that host inflammatory mediators alone can drive systemic pathological alterations [84]. Concurrently, metabolic disturbances in skeletal and cardiac muscle are closely associated with endothelial barrier disruption and immune dysfunction, thereby facilitating the transition from localized inflammatory injury to systemic pathology. Sepsis is therefore characterized by a complex and highly lethal pattern of multi-organ damage, with key pathological hubs including mitochondrial dysfunction, vascular barrier breakdown, and immune exhaustion. These pathological nodes not only reveal the underlying logic of disease progression but also represent potential targets for precision therapeutic interventions. For instance, recombinant angiopoietin-like protein 4 has been shown to significantly reduce vascular leakage, organ failure, and mortality in murine models of lethal sepsis and Neisseria meningitidis infection, further underscoring the critical role of endothelial barrier integrity in disease progression [85]. When the immune system is rapidly mobilized to combat infection, this protective response can escalate into a systemic storm of signaling mediators. Inflammatory cell death and cytokine release mutually reinforce one another, forming a self-sustaining inflammatory loop (**Figure 1**) that drives the progression of inflammation from local dysregulation to systemic inflammatory imbalance. Within this cascade, aberrant activation of immune cells together with uncontrolled release of inflammatory mediators becomes a central force sustaining the inflammatory response, thereby laying the mechanistic foundation for subsequent discussions on immune regulation and inflammatory signaling.

## 3 IMMUNE SYSTEM REGULATION IN INFLAMMATORY RESPONSES

### 3.1 Activation of immune cells and release of inflammatory cytokines

In sepsis-induced ALI and multiple organ dysfunction syndrome, the devastating cascade is mainly due to the abnormal activation of immune cells and the dysregulated release of inflammatory mediators, which triggers a harmful inflammatory cascade. Neutrophil-derived exosome miR-30d-5p was found to promote macrophage M1 polarization and pyroptosis, thus representing a critical element that drives lung injury [39].

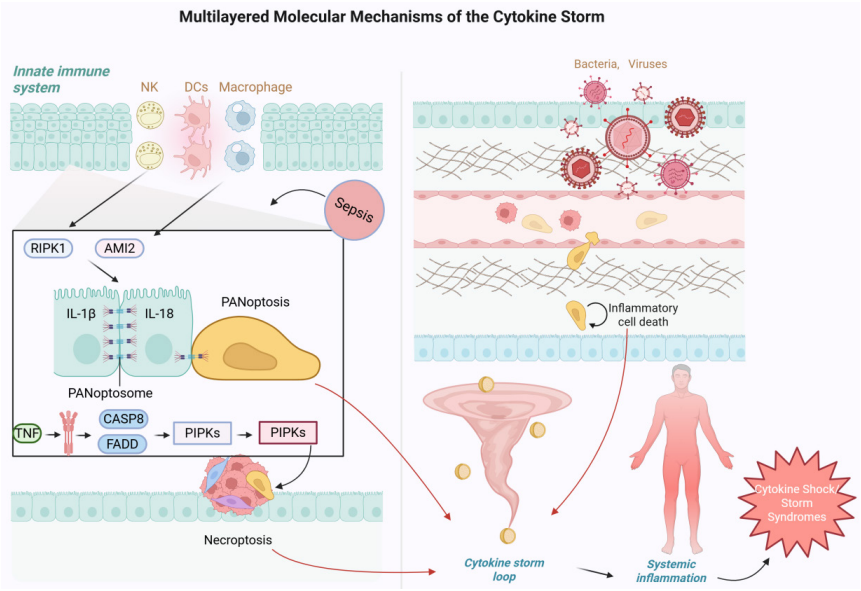


**Figure 1. Multi-layered molecular mechanism of inflammatory storm.** After pathogen invasion, the innate immune system is quickly activated by NK cells, dendritic cells and macrophages, inducing a vast amount of inflammatory mediators. This results in an inflammatory cascade focused on TNF, IL-1β and IL-18. The AIM2-dependent pathway works together with RIPK1 to promote the formation of the PANoptosis complex, including the assembly of PANoptosome components such as CASP8 and FADD, thus leading to inflammatory cell death and cytokine amplification. A variety of programmed cell death modalities, including pyroptosis and necroptosis, are interwoven to synergistically amplify tissue damage, as illustrated in the left panel of the figure, leading to the formation of the "cytokine storm loop". The right panel further depicts how inflammatory cell death and cytokine release disrupt tissue barriers and propagate inflammation systemically. Such a self-perpetuating inflammatory network can transgress tissue boundaries, producing a systemic inflammatory response and ultimately contributing to multiple organ failure and cytokine shock syndromes.Created by the authors using BioRender.

eCIRP facilitates the generation of aging neutrophils with augmented antigen presentation, leading to Th1 differentiation and IFN-γ–dependent accelerated high-level Neutrophil Extracellular Trap formation (NETosis). This amplifies the inflammation and damages tissues [86]. Furthermore, manganese ions also enhance lipopolysaccharide (LPS)-induced innate immune responses through activation of the cyclic GMP-AMP synthase–stimulator of interferon genes pathway, which leads to severe septic shock [87]. In the nervous system, septic plasma exosomes can induce microglial activation via TLR7/MyD88 signaling and result in neuroinflammation, which is associated with the pathogenesis of sepsis-associated encephalopathy (SAE) [88]. In addition to pro-inflammatory responses, protective physiological countermeasures are present in the body. S-phase kinase-associated protein 2 (Skp2) relieves tissue injury by suppressing ferroptosis in lung epithelial cells; deletion of G protein-coupled receptor 174 (GPR174) enhances regulatory T cell (Treg) function and M2 macrophage polarization, thereby inhibiting excessive inflammation [89, 90]. Furthermore, DPP4 and TXN have been suggested as probable indicators for immune-regulation functions, which can offer new molecular targets for precision therapy [91].

The intersection of metabolism and inflammation is also important. Tripterygium wilfordii glycosides inhibit the Warburg effect via PKM2/high mobility group box 1 (HMGB1), which attenuates inflammation and organ damage, while neutrophil extracellular traps (NETs) promote ferroptosis by Methyltransferase-Like (METTL)3-mediated N6-methyladenosine ($m^6A$) modification of Glutathione Peroxidase 4 (GPX4), aggravating lung injury [92, 93]. In addition, interactions among inflammatory factors are also important. TNF-α and IFN-γ induce PANoptosis through the JAK/STAT1/IRF1 axis to cause severe cell death and tissue damage. This process is also observed in COVID-19 and sepsis [94]. On the other hand, the lactate-enhanced qSOFA score has shown good predictive value for in-hospital mortality in patients with sepsis; mechanistically, LPS/IFN-γ inhibit PTEN-induced kinase 1 (PINK1)-mediated mitophagy through the STAT1-caspase pathway, thereby promoting mitochondrial reactive oxygen species production, bacterial clearance, and improved survival during sepsis [13, 44].

Immune activation in sepsis occurs through multiple layers of pro-inflammatory amplification, including extracellular exosomal miRNAs, NET formation, and PANoptosis, which collectively drive acute organ injury. However, persistent inflammatory stress progressively reprograms immune regulatory networks, shifting the host response from hyperinflammation toward immune exhaustion and dysregulation. This transition ultimately leads to the immune imbalance that defines the later stages of sepsis.

### 3.2 Immune system imbalance and hyperreaction

Following this storm of inflammation, there is a rapid transition toward an immunosuppressive state in sepsis patients, with the establishment of a classic "immune imbalance". Reduced expression of HLA-DR on monocytes is a hallmark of this stage and is strongly related to poor prognosis [95]. In terms of molecular mechanisms, p53 stimulates immunosuppression through inhibition of $CD4^+$ T cell proliferation and upregulation of apoptotic pathways, ultimately disrupting T cell homeostasis; the absence of Sulf-1 alters endothelial heparan sulfate modifications, resulting in glycocalyx dysfunction that mediates pulmonary immunosuppression [96, 97]. The emerging role of non-coding RNAs in regulation of

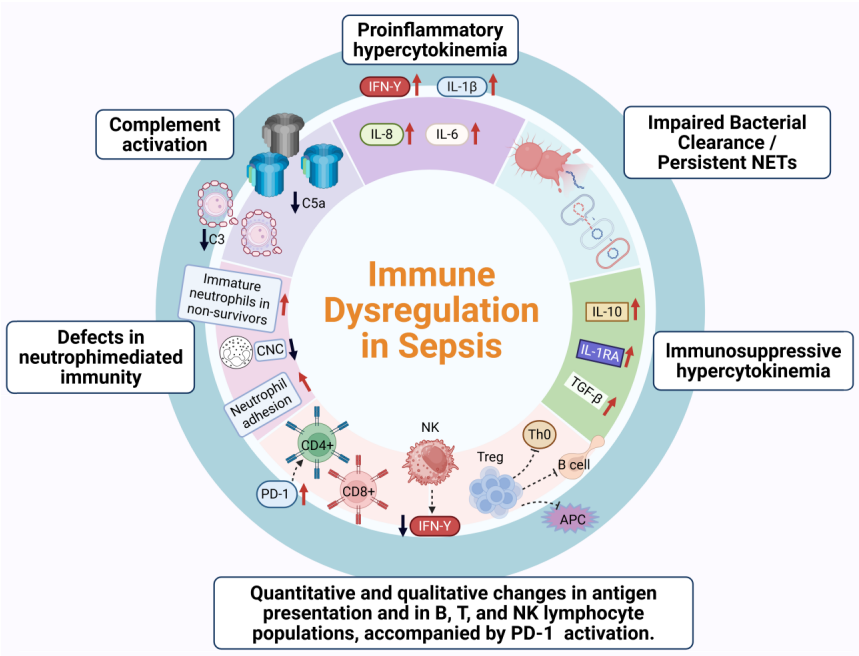


**Figure 2. Pathophysiological mechanisms of immune imbalance in sepsis.** The immune dysregulation induced by sepsis is a biphasic response in which proinflammatory and immunosuppressive phases succeed each other, as illustrated in the circular schematic showing interconnected immune pathways. At the very beginning, over-activation of the complement system (C3, C5a) and neutrophil dysfunction amplify inflammation to an overwhelming level, as exemplified by a dramatic rise in factors like IL-1β, IL-6 and IFN-γ, corresponding to the upper proinflammatory hypercytokinemia segment. Then, immunosuppressive cytokines (IL-10, IL-1RA, TGF-β) release follows, leading the host into a condition of immune exhaustion and chronic infection, as depicted in the right immunosuppressive hypercytokinemia segment, which is also associated with impaired bacterial clearance and persistent NETs. Alterations of B, T and NK lymphocytes in terms of their numbers and quality, as well as uncontrolled activation of the PD-1 pathway, together represent patterns most likely to lead to failed antigen presentation and subsequent immune paralysis, as shown in the lower portion of the figure highlighting lymphocyte dysfunction. This depicts a time-dependent progression of systemic inflammation to immunosuppression that forms the unmodifiable pathological basis for sepsis. Created by the authors using BioRender.

immune response has been recently highlighted. lncRNA Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) modulates polymorphonuclear myeloid-derived suppressor cell (PMN-MDSC) differentiation via STAT3 phosphorylation, and its dysregulation enhances immunosuppressive functions [98]. Meanwhile, MLIP alleviates excessive inflammatory responses by regulating macrophage metabolism and oxidative stress, providing a potential target for restoring immune balance [99]. In dendritic cells, SREBF1 mediates lipid metabolism reprogramming and endoplasmic reticulum stress, thereby driving immune paralysis and further locking the body into an immunosuppressive state [100].

The diversity of immunotypes has also been confirmed by population-based studies. Transcriptomic analysis divides sepsis into two subgroups, SRS1 (immune-suppressive type) and SRS2 (predominantly proinflammatory type). SRS1 is classically defined by low HLA-II and T cell exhaustion, and is strongly associated with lower survival rates [7]. Persistent upregulation of immune checkpoint molecules, including PD-L1–related inhibitory pathways, contributes to T cell exhaustion and impaired antiviral responses, reinforcing the immunosuppressive phenotype in sepsis [81, 101, 102].

Therapies targeting immune exhaustion have shown promise. Nicotinamide riboside supplementation has been shown to partially restore T cell function via activation of $NAD^+$/SIRT1 signaling pathways, restore immune response, and decrease organ injury and mortality [103]. However, in elderly patients, prolonged elevation of IL-6 and increased T cell exhaustion contribute to a more sustained immunosuppressive state that is less amenable to intervention [104]. Notably, ILC2-derived IL-13 secretion in response to PD-1 deficiency partially reversed long-term muscle weakness and increased gene expression in the skeletal muscle. This indicates a strong relationship between immunosuppression and long-term functional deficits [105].

In the escalating inflammatory cascade, the immune response shifts toward a biphasic dysregulated state characterized by concurrent hyperactivation and immunosuppression. Crosstalk between pro-inflammatory and immunosuppressive signals shapes a complex immune landscape (**Figure 2**), driving sepsis progression and the transition of host defense from coordinated activation to dysregulated exhaustion. Within this network, diverse inflammatory mediators regulate intercellular communication, immune activation, and feedback control. For example, the monocyte-associated molecules CAP-1 and IL-16 participate in cell–cell communication in sepsis and septic shock and have been proposed as potential diagnostic biomarkers [106]. Elucidating the roles of inflammatory mediators in this regulatory network may therefore provide insights into sepsis pathophysiology and therapeutic targeting.

### 3.3 The role of inflammatory mediators in sepsis

Inflammatory mediators in sepsis function as a double-edged regulatory network that amplifies immunity while inducing negative regulation. Pyroptosis-related extracellular vesicles (pyroEVs) carrying membrane-expressed ASC proteins attach to B cells and suppress TLR4 signaling, reducing overactivated inflammation. This indicates that vesicle-mediated interventions might be of potential therapeutic value [107]. In contrast,

ferritin promotes NETosis in an MSR receptor-dependent manner via the Peptidylarginine Deiminase 4 (PAD4)/NE/ROS pathway, resulting in aggravated cytokine storm and lung injury, marking its important pro-inflammatory role in the process [108].

Among inflammatory cytokines, higher levels of MIP1α and IL-1ra are associated with lower mortality, suggesting that some mediators may counterbalance dysregulated inflammatory responses and serve as potential therapeutic targets [109]. Dexmedetomidine exerts protective effects on neuroinflammation and blood-brain barrier disruption by promoting astrocyte α2A receptor activation, implying the dynamic homeostasis of inflammatory regulation circuits between inflammation and the nervous system [110]. The enrichment of $CD14^{+}CD16^{+}$ monocytes in the blood, on the other hand, correlates tightly with increased susceptibility, severity, and mortality in sepsis, highlighting an essential role for disequilibrium among cellular populations in immunopathology [111].

Both genetic and clinical investigations support the predictive and stratification value of inflammatory variables. TNF-α -308 AA genotype or the carriers of the A allele is associated with higher serum TNF-α levels, and may serve as a genetic predictor of inflammatory responses [112]. Plasma TNF-α levels in septic patients are about 10 times higher than those in healthy individuals [113]. The TNF-α -308G/A polymorphism and IL-6 levels do not correlate with mortality in neonatal sepsis, although the prediction capacity may be heterogeneous in the population and age [114]. Of interest, TNF-α level was significantly higher in children with positive blood cultures, particularly those with Gram-negative bacterial infection and could be another alternative marker for early intervention [115]. Moreover, elevated levels of IL-6 and IL-8, as well as of KC-like and Regulated upon Activation, Normal T Cell Expressed and Secreted (RANTES), have been observed in experimental models, demonstrating the conservation of inflammatory mediators during immunopathology and their application to clinical research [116].

Inflammatory mediators in sepsis not only drive the cytokine storm and organ injury but also provide important clues for risk prediction, patient stratification, and precision therapies. The production and immunoregulatory functions of these mediators rely on the activation of multiple cellular signaling pathways, which play critical roles in inflammatory amplification, immune imbalance, and organ damage. Within this complex signaling network, N-myc and STAT interactor (NMI) has been identified as an important regulator that integrates inflammation-related signals from multiple receptors. Studies have shown that NMI participates in immune signaling through receptors such as IFNAR1, TNFR1, and TLR family members, and is closely associated with the activation of NF-κB, MAPK, and JAK pathways, thereby promoting pro-inflammatory cytokine expression and enhancing inflammatory responses [117]. Among these pathways, Toll-like receptor (TLR) signaling represents a central mechanism linking pathogen recognition to downstream inflammatory cascades in sepsis.

## 4 SIGNAL TRANSDUCTION PATHWAYS IN SEPSIS

### 4.1 TLRs and signaling cascades

As the central sensors of the innate immune system, TLRs are essential in promoting sepsis-associated inflammatory storm and immune dysregulation. Their signaling pathways are critical not only for pathogen recognition but also for inflammasome activation, metabolic imbalance, and organ failure during sepsis. There is abundant experimental and clinical data demonstrating that TLR signaling pathways play a dual role in amplifying inflammation and mediating therapeutic intervention. Fh15 protein derived from a parasite and small molecule inhibitor TAK-242 effectively inhibit LPS-induced inflammation and tissue injury, which indicates that TLR4 can be a therapeutic target [118, 119]. In parallel, both bacterial mRNA and LPS work in concert to activate the NLRP3 inflammasome, with NLRP6 also undermining host defense by sensitizing T cells through the IL-18 release. This implies a complicated interrelation and potentiation of TLR signaling by inflammasomes [120, 121].

At the systemic level, the MyD88–NF-κB–TNF-α pathway manifests a rapid phase-specific activation pattern in response to polymicrobial infection while malignant fibrous histiocytoma amplified sequence 1 presented the features of early inhibition combined with late progression along the TLR2 pathway. Such observations allow for a temporal view of the course of sepsis [122, 123]. Furthermore, serum amyloid A (SAA) acts via TLR2/TLR4 to transform HDL into pro-inflammatory particles, enhancing vascular inflammation. The elevated expression of genes like LCN2 and ELANE also support a role of TLR pathways in the immune dysregulation [124, 125]. Of note, the contribution of TLR signaling goes beyond inflammation and affects metabolism and endocrinology. TLR4/MD2-mediated LPS suppresses the growth hormone receptor, demonstrating its distinctive role in metabolic adaptation during sepsis [126]. In contrast, the transcription factor ZBTB20 enhances tissue damage through augmented activation of NF-κB. Its depletion greatly ameliorates inflammatory injury, thus emerging as a novel therapeutic target [127].

TLR-associated signaling pathways are not only central initiators of the inflammatory storm in sepsis but also important links between immunosuppression and metabolic disorders. A comprehensive exploration of their dynamic properties and their interplay mechanisms may establish the basis for the discovery of the intact landscape of disease development, as well as novel strategic avenues for stratified management and precision intervention in sepsis.

### 4.2 Cytokine storm and signal amplification

Excessive cytokine production represents a hallmark of immune dysregulation in sepsis, and failure to contain signal amplification contributes to systemic inflammation and multiple organ failure. Research has indicated that TNF-α and IFN-γ may cooperatively facilitate PANoptosis depending on the JAK/STAT1/IRF1 axis, which can be responsible for the deadly inflammatory cascade in COVID-19 and sepsis [94]. The systemic inflammatory response syndrome in fetal sepsis is responsible for multiple organ dysfunctions and is directly linked to severe neonatal morbidity, sepsis-related mortality and long-term sequelae risk [128]. It has also been shown that the combined action of pro-inflammatory cytokines like TNF and IL-18 can mirror many systemic effects of sepsis, leading to pervasive rewiring in both gene transcription and cellular composition that amplifies tissue destruction [84].

In the past few years, the targeting/inhibition of inflammation-induced cell death has been proposed as one of the major advances in controlling cytokine storms. Rapamycin has been reported to alleviate endothelial injury by promoting autophagy while suppressing gasdermin D (GSDMD)/caspase-1-mediated pyroptosis and decreasing the production of pro-inflammatory cytokines IL-1β, IL-18 [129]. The caspase-1 inhibitor AC-YVAD-CMK can also ameliorate acute kidney injury (AKI) by inhibiting the NLRP1/GSDMD pathway [130]. In contrast, the MSR-dependent PAD4/NE/ROS pathway in macrophages triggers NET formation in response to high levels of ferritin and promotes inflammation and lung injury, representing a mediator of poor prognostic significance [131].

The immunological features of cytokine storms vary across diseases. Sepsis and hemophagocytic lymphohistiocytosis (HLH) are diseases of overwhelming inflammation, but in contrast to sepsis patients, HLH patients show significant overactivation of CD38high/HLA-DR$^+$ effector T cells, primarily CD8$^+$ T cells. Conversely, this phenotype is not seen in early sepsis, providing a molecular rationale for the clinical distinction between the two entities [132]. Moreover, the Epidermal Growth Factor Receptor can transactivate and induce production of TNF-α in cardiomyocytes through the TACE/TGF-α pathway. Its inhibitor has been demonstrated to potently reverse heart dysfunction in animal subjects and supports the existence of druggable signaling nodes in the myocarditis inflammation network [133].

Additional layers of regulatory axes are also being uncovered. The hepatocyte Pannexin 1 (PANX1)–IL-33 axis is triggered by the ATP–P2X7 pathway, leading to ST2$^+$ Treg infiltration. This axis acts as a negative regulator for inflammation amplification, attenuating endotoxin-induced liver injury [134]. Resveratrol inhibits the microglial NLRP3/IL-1β axis via receptor-dependent mechanisms, improving cognitive function in SAE; phosphodiesterase 10A inhibitors suppress pyroptosis and organ damage by inhibiting NLRP3 inflammasome activation, providing a new idea for neuroprotection [135, 136]. Furthermore, the natural product EGCG may ameliorate inflammation and ferroptosis by dampening RELA activity and suppressing exaggerated macrophage activation, indicating that plant-derived molecules may have therapeutic potential for inflammation-related intervention [137]. IL-6 signaling, as another core pathway, regulates microtubule dynamics through the JAK2/Ninein axis, thereby promoting Extracellular Signal-Regulated Kinase (ERK) 1/2-mediated phosphorylation of p47$^{phox}$ and LC3-associated phagocytosis. Its deficiency leads to immune paralysis and dysfunction of monocytes/macrophages [138]. This finding not only demonstrates the dynamic changes of inflammation amplification and immune hyporesponsiveness, but also offers a novel mechanistic basis for precision intervention.

Cytokine storms drive uncontrolled inflammation and multi-organ injury in sepsis, and their cross-pathway amplification reflects the dynamic imbalance between excessive immune activation and compensatory immunosuppression. Computational modeling that captures key signaling nodes and their spatiotemporal dynamics has emerged as a valuable framework for understanding these complex inflammatory networks and identifying potential therapeutic targets. In particular, agent-based modeling (ABM) has been applied to simulate systemic immune responses and to explore fundamental mechanisms of sepsis pathogenesis [139]. Persistent immune dysregulation is accompanied by profound phenotypic and functional remodeling of immune cells, including alterations in metabolic programs, differentiation trajectories, and signaling regulation, collectively shaping the systemic landscape of immune exhaustion (**Table 2**). **Table 2** summarizes the major functional switches and signaling perturbations of key immune cell populations during sepsis, providing a cellular framework for understanding immune imbalance and setting the stage for further discussion of immune cell–specific regulatory mechanisms.

### 4.3 Negative feedback mechanisms and immune homeostasis

In addition to the systemic uncontrolled inflammatory response, sepsis is also characterized by the activation of various negative feedback mechanisms that serve to curb tissue damage and maintain immune homeostasis. Inhibition of NLRP3 inflammasome activation and pyroptosis by certain metabolic products of myeloid cells, including itaconate, promotes inflammatory tolerance and limits tissue damage [167]. Serum exosomes have a dynamic molecular pattern in the progression of disease and their correlation with inflammatory, coagulation and vitamin metabolism pathways makes them a new approach to integrate diagnosis and therapy [168].

**Table 2. Cellular characteristics of immune dysregulation in sepsis**

| Cell type | Phenotypic/functional alterations | Mechanistic features | Clinical consequences | Potential interventions | References |
|---|---|---|---|---|---|
| Monocytes | Enhanced anti-inflammatory response accompanied by the induction of long-lasting innate immune memory (trained immunity) | IL-4 suppresses acute inflammation and promotes trained immunity | Increased risk of opportunistic infections, morbidity, and mortality | Apolipoprotein A1–IL-4 fusion protein nanoparticle–based targeted therapy | [140] |
| Dendritic cells | Reduced expression of costimulatory molecules | Cytosolic mtDNA mediates immune paralysis via activation of the STING signaling pathway | Contributes to sepsis-associated immunosuppression and worsened prognosis | Hydrolysis of mtDNA or STING deficiency reverses immune paralysis and improves prognosis | [141] |
| Macrophages | NET formation is initially suppressed followed by delayed clearance, leading to impaired macrophage efferocytic function | Alcohol disrupts the processes of NETosis and efferocytosis | Exacerbates sepsis-associated liver injury | Neutrophil depletion alleviates LPS-induced inflammation and hepatic injury | [142] |
| Neutrophils | Abnormally elevated formation of NETs | Increased Padi4 expression and enhanced citrullination of histone H3 | Exacerbated organ injury, intensified inflammation, and aggravated sepsis severity | Degradation of NETs using rhDNase or PAD-4 inhibitors | [143] |
| Microglia | Increased NET release, blood-brain barrier disruption, and neuronal apoptosis | Nuclear translocation of PD-L1 promotes p-Y705-Stat3–driven transcription of GSDMD | Leads to SAE and memory impairment | Therapeutic strategies include anti–Gr-1 antibody, DNase I, or targeting GSDMD/PD-L1 | [144] |
| $CD4^+$ Tregs | V-domain Immunoglobulin Suppressor of T-cell Activation (VISTA) deficiency reduces Treg abundance but enhances their activity, exacerbating inflammation | The immune checkpoint VISTA exerts protective effects by modulating Tregs | Markedly reduced survival, accompanied by aggravated organ injury and inflammation | Strategies include enhancing VISTA expression or adoptive transfer of $VISTA^+$ Tregs | [145] |
| Macrophages | Enhanced aerobic glycolysis and overactivation of the inflammasome | PKM2 promotes inflammasome activation via modulation of Eukaryotic translation initiation factor 2α kinase 2 (EIF2AK2) phosphorylation | Leads to lethal endotoxemia and sepsis | Pharmacological or genetic inhibition of PKM2 or EIF2AK2 | [146] |
| T lymphocytes | Reduced lymphocyte apoptosis and suppressed cytokine production by macrophages | The VISTA immune checkpoint transmits inhibitory signals | Enhanced bacterial clearance, mitigated organ injury, and improved survival | Treatment with high-affinity anti–VISTA antibody (MH5A) | [147] |
| Cardiomyocytes | Significantly increased succinylation of Voltage-Dependent Anion Channel 2 (VDAC2) protein | Succinyl-CoA induces succinylation at VDAC2 K46, triggering ferroptosis | Leads to SIMD | Therapeutic interventions include ND-630 or mitochondria-targeted nanoparticle TPP-AAV | [148] |
| Renal tubular epithelial cells (HK-2 cells) | Enhanced aerobic glycolysis, increased lactate production, and suppressed autophagy | Lactate inhibits autophagy by downregulating the SIRT3/p-AMPK pathway | Leads to SI-AKI | Treatment with the aerobic glycolysis inhibitor 2-DG | [149] |
| Pulmonary epithelial cells | Reduced Skp2 expression and impaired membrane localization of Solute Carrier Family 3 Member 2 (SLC3A2) | MEK/ERK pathway suppresses Skp2, decreases SLC3A2 ubiquitination, and triggers ferroptosis | Leads to sepsis-induced ALI | Intravenous administration of lipid nanoparticles (LNP) encapsulating Skp2 mRNA | [89] |
| BM cells | Persistent production of proinflammatory cytokines and hyperresponsive phenotype | METTL14 deficiency reduces SOCS1 $m^6A$ methylation, leading to decreased SOCS1 levels | Bacterial infection results in high mortality | Forced expression of SOCS1 rescues the hyperresponsive phenotype | [150] |

| | | | | | |
|---|---|---|---|---|---|
| Hepatocytes | Exacerbated cytokine storm and dysregulated immune response | PANX1 positively regulates IL-33 synthesis via the ATP-P2X7 pathway | Worsens endotoxemia and post–liver transplant hepatic injury | Therapeutic approach involves recombinant IL-33 targeting ST2$^+$ Tregs | [134] |
| Pulmonary endothelial cells | Elevated Histone H3 lysine 14 lactylation (H3K14la), leading to endothelial activation and ferroptosis | Glycolysis-derived lactate induces H3K14la, promoting expression of ferroptosis-related genes | Leads to sepsis-induced ARDS | Inhibition of glycolysis or H3K14la to block ferroptosis | [151] |
| Pulmonary epithelial cells | Upregulated Olfactomedin 4 (OLFM4) expression suppresses LPS-induced proinflammatory responses | OLFM4 inhibits the LDHA/NF-κB pathway by reducing ROS and HIF1α levels | Modulates sepsis-associated ARDS | Therapeutic approaches include recombinant OLFM4 or OLFM4 overexpression | [152] |
| T cells | Increased T cell infiltration and decreased dendritic cell infiltration | Lysosomal metabolic dysregulation is associated with an imbalanced immune microenvironment | Contributes to sepsis and ARDS | CTSO and HLA-DQA1 may serve as novel diagnostic and therapeutic targets | [153] |
| Pulmonary fibroblasts | Suppressed Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha (PGC-1α) expression and increased release of mitochondrial DNA-containing microparticles | Mitochondrial dysfunction drives mitochondrial DNA-containing microparticle–induced MMT | Facilitates the progression of SAPF | Activation of PGC-1α alleviates fibrosis, representing a potential therapeutic strategy | [154] |
| Renal tubular epithelial cells | Attenuated ferroptosis with increased GPX4 expression | NRF2 nuclear translocation upregulates GPX4 expression, inhibiting ferroptosis | Alleviates SI-AKI | Treatment with melittin, the main component of bee venom | [155] |
| CD64$^+$ immature neutrophils (CD123$^+$ and PD-L1$^+$ subsets) | Two novel subsets emerge with impaired activation and phagocytic functions | The proportion of CD123$^+$ neutrophils correlates with clinical severity | Useful for specific diagnosis of sepsis and differentiation from other inflammatory conditions | Rapid diagnosis and therapeutic guidance via blood testing using seven markers | [156] |
| Neutrophils (CXCR2$^+$ and CD274$^+$IL1RN$^+$ subsets) | Markedly increased neutrophils exhibiting an immunosuppressive phenotype | Mechanistic feature: developmental trajectory from CXCR2$^+$ to CD274$^+$IL1RN$^+$ subsets | Leads to pulmonary immunosuppression, increasing the risk of secondary infections and mortality | CXCR2 blockade reduces PD-L1$^+$ neutrophils and improves survival | [157] |
| CD8$^+$ T cells | Increased platelet MHC-I expression with enhanced antigen cross-presentation capacity | Platelets modulate CD8$^+$ T cells via MHC-I–mediated antigen cross-presentation | Impairs CD8$^+$ T cell function and correlates with sepsis mortality | Targeting platelet MHC-I improves CD8$^+$ T cell responses and survival | [158] |
| T lymphocytes | Decreased neutrophil apoptosis and increased T lymphocyte apoptosis | HMGB1 upregulates neutrophil PD-L1 via TLR2, engaging T cell PD-1 | Leads to immunosuppression and sepsis-induced lung injury | Therapeutic interventions include GA or the TLR2 inhibitor C29 | [102] |
| ILC2s | ILC2 activation with increased secretion of IL-5 and IL-13 | IL-33 induces IL-5 secretion by ILC2s, protecting cardiomyocytes | Alleviates sepsis-induced cardiac dysfunction and myocardial injury | Therapeutic strategies include IL-33 supplementation or harnessing ILC2 function | [159] |
| Neutrophils | Elevated HMGB1 lactylation with increased formation of NETs | Lactate promotes HMGB1 lactylation via macrophage-derived exosomes, activating the cGAS/STING pathway | Exacerbates SA-AKI | HMGB1 may serve as a potential therapeutic target for SAKI intervention | [160] |
| NK cells | Increased monocytes and decreased inactive NK cells | Coagulation-related genes are involved in immune activation, antigen processing, and other pathways | Contributes to sepsis-induced organ dysfunction | FCER1G and FYN may serve as diagnostic biomarkers and therapeutic targets | [161] |

| | | | | | |
|---|---|---|---|---|---|
| Macrophages | Low expression of ferroptosis-related gene Lipin 1 (LPIN1) with increased macrophage infiltration | LPIN1 downregulation is associated with inflammation and immune response pathways | Leads to poor prognosis and reduced survival in sepsis patients | LPIN1 may serve as a prognostic biomarker and potential therapeutic target | [162] |
| T cells | Elevated soluble urokinase-type plasminogen activator receptor (suPAR) levels with increased renal T cell infiltration, exacerbating inflammation | suPAR promotes T cell–mediated renal inflammation by upregulating chemokines | Leads to more severe SI-AKI, increasing the need for RRT and mortality risk | suPAR deficiency ameliorates SI-AKI, indicating it as a potential therapeutic target | [163] |
| Hippocampal neurons | Upregulated Fgr expression associated with neuroinflammation, oxidative stress, and mitochondrial dysfunction | Fgr inhibits SIRT1 activity, subsequently affecting the PGC-1α pathway | Leads to SAE and cognitive-emotional dysfunction | Fgr kinase inhibitors confer protection by activating the SIRT1/PGC-1α pathway | [164] |
| Hepatocytes | Marked upregulation of S100A8/A9 with hepatic dysfunction and mitochondrial impairment | S100A9 inhibits the AMPK pathway, affecting fatty acid and glucose metabolism | Leads to sepsis-induced ALI | S100A9 inhibitor Paquinimod (Paq) can prevent liver injury and mortality | [165] |
| Liver macrophages | Hepatocyte mitochondrial structure and energy supply are impaired, accompanied by altered TREM2 expression | TREM2-deficient macrophages release exosomes containing miR-106b-5p, inhibiting Mfn2 | Nonalcoholic fatty liver disease (NAFLD) increases susceptibility to sepsis and mortality | Overexpression of TREM2 in liver macrophages improves hepatic energy supply and sepsis outcomes | [166] |

Perturbations in immune homeostasis are associated with disease progression. Silencing Cystatin C accelerates LPS-induced inflammation by inhibiting autophagy and increasing caspase-11 expression, which enhances NLRP3 inflammasome activation [169]. T-cell lymphoma breakpoint-associated target genes and Sestrin 2 boost host resistance and disease tolerance by inducing autophagy and mitochondrial quality control, which increases clearance of bacteria but attenuates organ damage [136, 170]. These data demonstrate that autophagy-associated pathways are central hubs for fine-tuning inflammation versus tissue protection.

In terms of signaling regulation, S100A10 inhibits the TLR pathway to downregulate excessive inflammation, and lack of it increases immune damage [171]. Membrane-bound MHC I molecules feed back to suppress TLR signaling through the Fps–SHP-2 pathway to provide self-restricted protection of innate immunity [172]. Meanwhile, immunosuppression may stem from imbalanced endogenous negative feedback, whereby SAMSN1 promotes an immune-suppressive state that can be reversed upon its depletion [173]. APE1 deficiency impairs macrophage phagocytic ability via the GSK3β/Nrf2 axis, contributing to bacterial infection and immune defects [174]. Notably, TSLP signaling serves as a central protective factor for myeloid cells. Its absence does not impair bacterial eradication, but exacerbates systemic inflammation and organ injury. By contrast, the survival of mice is significantly enhanced by TSLP-mediated suppression of hyperactivation of myeloid cells [8].

While dysregulated signaling cascades orchestrate the acute immune and metabolic responses in sepsis, inter-individual variability in these pathways is profoundly influenced by inherited genetic variations. Genome-wide association studies have identified several low-frequency variants associated with reduced 28-day survival in sepsis, including a missense variant in SAMD9 (hazard ratio [95% CI]=1.64 [1.37–6.78], $P=4.92\times10^{-10}$), a gene implicated in inflammatory responses that may mediate tissue injury [175]. In parallel, integrative genetic analyses incorporating Mendelian randomization have identified multiple candidate genes significantly associated with sepsis susceptibility, several of which remained robust after sensitivity analyses. These findings collectively highlight the contribution of host genetic variation to disease susceptibility and prognosis [176]. Thus, integrating host genetic architecture into the framework of signaling networks provides an essential dimension for understanding disease heterogeneity and differential clinical outcomes. Importantly, many of these genetically influenced pathways also generate measurable molecular signatures that are increasingly investigated as emerging biomarkers for diagnosis, risk stratification, and prognosis in sepsis.

## 5 HOST GENETIC FACTORS AND SUSCEPTIBILITY TO SEPSIS

### 5.1 Genetic polymorphisms and individual differences

Host genetic variations play a critical role in sepsis susceptibility and outcomes, affecting various aspects ranging from pathogen recognition and immune responses to metabolic homeostasis and organ injury. Matrix metalloproteinase (MMP) 8 rs11225395 G/G genotype is associated with sepsis susceptibility, and MMP1 and MMP3 are not only linked to

bacterial and viral infection susceptibility but also to agent-specific levels of severity. This indicates that the genetic variation of the host plays a role in pathogen-specific patterns of immune defense [177]. Gene-based analyses have also demonstrated that sepsis-2 and the Sepsis-3 criteria not only have a polygenic overlap but also possess unique molecular attributes. Their multigene risk scores also have a high predictive value, suggesting that sepsis susceptibility usually results from the combined effect of multiple small-effect polymorphisms [178].

The interplay of genetic susceptibility and environmental factors has been given more attention in research. For instance, genetic insomnia is positively associated with sepsis risk, and this link is in part explained by cardiac metabolism pathways involving heart function. This indicates that sleep disturbances may be a targetable genetic risk factor [179]. Alterations of the coagulation and complement cascades contribute significantly to the disease course. Polymorphisms in the THBD gene are strongly associated with AKI risk and death [180]. A gain-of-function variant in cholesteryl ester transfer protein (CETP) is associated with increased acute sepsis mortality, whereas genetic evidence for decreased CETP function, together with pharmacological CETP inhibition in humanized mouse models, suggests potential survival benefits through the preservation of HDL-C levels [181]. Different variants of complement C5 can either reduce susceptibility or, conversely, accelerate disease progression by enhancing C5a generation and the release of pro-inflammatory mediators [182].

Immunity- and metabolism-related pathways also serve as hub nodes that regulate the disease. The VDR Fok I polymorphism is a strong risk factor for sepsis, and it correlates positively with lower vitamin D status, thus indicating that the vitamin D metabolic axis may represent an important host regulatory pathway [183]. In patients with diabetes, an association was found between Monocyte Chemoattractant Protein-1 (MCP-1) rs1024611 G allele and susceptibility to sepsis, which may be attributed to upregulated expression of MCP-1 and TNF-α [45]. High-risk allele combinations of TNFA rs1800629 and TLR4 rs4986791 in trauma patients are associated with significantly increased risk of sepsis, considering that TLR4 is a prognostic variant [184]. Moreover, although the reported associations of certain polymorphisms in genes including CHRNA7, NR5A2 and SUFU with sepsis-associated acute kidney injury (SA-AKI) have not shown genome-wide significance, these findings underscore the influence of host genetic differences on disease phenotype [185]. Polymorphisms in inflammation-related genes provide broader mechanistic insights. The elevated serum and urinary IL-10 levels in carriers of the IL-10 rs1518111 T allele are strongly associated with the development of SA-AKI, demonstrating that both inflammatory factor levels as well as genetic susceptibility play critical roles in the risk of organ damage [186]. Furthermore, PCSK9 loss-of-function not only increases organ injury by altering lipoprotein metabolism and removal of endotoxins but also impairs endothelial function by regulating Angpt-1, thereby aggravating septic pathology [187].

Susceptibility to sepsis is not monogenic but due to the combined action of multiple pathway variants. Such effects include inflammation control, immunological response, coagulation deregulation and metabolic perturbation. A comprehensive investigation of the dynamic properties and interaction mechanisms in these genetic networks can not only help uncover the molecular pathogenic basis for sepsis susceptibility, but also serves as an essential framework for developing risk prediction models and precision intervention strategies.

### 5.2 Gene expression regulation and inflammatory response

Inflammatory dysregulation in sepsis does not ensue from a single signal but rather represents a systemic disorder arising as a consequence of the perturbation of transcriptional homeostasis, abnormal epigenetic changes and malfunctioning noncoding RNA networks. It has been reported that the disproportion of expression of TLR4 and GRP78 is closely related to patient prognosis, indicating their dynamic properties during abnormal inflammatory responses and their potential to serve as monitoring parameters [188]. At a much deeper level, however, the transcription factor PU.1 induces MDSC differentiation and aggravates immune suppression via lncRNA Hotairm1 and its related epigenetic modification network. This connects transcription factors, epigenetic marks and immune dysregulation in a coordinated manner [189]. Additionally, the function of $m^6A$ methylation in immune cell infiltration and Th17 differentiation is receiving more attention. Master factors, such as METTL16 and IGF2BP1, were demonstrated to be involved in the progression of the late inflammatory phase, strongly suggesting the utility of epigenetic manipulation [190].

Multivariate complexity of gene regulatory networks in organ injury varies across different organs. Adenosine-uridine RNA editing of neuronal gene Grik2 and Flna in SAE are involved in the development of cognitive deficits. This phenomenon exhibits age- and sex-specific traits [191]. Research on natural compounds has discovered new ways of modulating inflammation and oxidative stress.Vitexin relieves lung injury in part through the SNHG1/DNA methyltransferase (DNMT) 1/miR-495 axis, while Gossypol alleviates myocardial injury via HDAC inhibition and histone acetylation remodeling [192, 193]. Furthermore, exosomes and non-coding RNAs were found to be implicated in immune reprogramming. Microvesicles derived from patients can deliver DNMT1/3A, which results in hypermethylation of the TNF-α promoter and immunosuppression [194]. circMAPK1 promotes NLRP3 inflammasome activation through modulating demethylation, which worsens lung injury [195]. On the other hand, miR-221-5p enhances inflammatory responses by inhibiting mitophagy and promoting organ damage as well [196].

The widespread involvement of $m^6A$ modification in sepsis-induced multiple-organ injury is noteworthy. METTL3-triggered methylation has been reported to promote liver injury progression, but in the heart, lncRNA and mRNA expression differences lead to functional decline through the TNF and PI3K-Akt signaling pathways [197, 198]. In AKI, the NF-κB/miR-376b/NFKBIZ negative feedback system not only controls inflammation and cell death but also shows the diagnostic significance of urinary miR-376b [199].

Gene regulatory networks of sepsis have global characteristics with complex coupling between multiple hierarchical levels, pathways, and organs. In this dynamic, feedback-loop-driven environment, inflammation potentiation and immune dysfunction maintain a parallel course, leading to multi-organ failure. More detailed exploration of these mechanisms not only uncovers the molecular basis of sepsis but also provides a basis for precision therapy and personalized medicine.

### 5.3 Clinical significance of emerging biomarkers

Advances in novel biomarkers are reshaping the diagnosis and treatment of sepsis. Evidence from the endocrine and metabolic aspects suggests that using T3 within the 60–80 ng/dl range is related to lower incidence rates of Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS), whereas profound T3 deficiency in combination with high Sequential Organ Failure Assessment (SOFA) scores predicts poor outcomes [200]. Metabolomic studies have indicated the potential causal role of dysregulation of the glycolysis/pyruvate pathway in the risk and prognosis of sepsis, which can lay a strong foundation for developing metabolic biomarkers for early diagnosis [201].

Genetic and immune biomarkers also show significant clinical utility. In patients, individuals with the LAG-3 rs951818 AA genotype were found to have a reduced risk of death, suggesting their potential value as a prognostic genetic marker [202]. Furthermore, molecular fingerprints of IRRGs perform well in identifying high-risk individuals and monitoring immune status, paving the way for precise intervention [203]. Synergistic detection of inflammatory mediators has also improved clinical prediction models. IL-10 levels integrated with the National Early Warning Score (NEWS) score further enhances sensitivity in early detection of sepsis risk, and the combined measurement of urinary CRP, α1-acid glycoprotein and SAA dramatically improves discrimination between sepsis and SIRS [204, 205]. In addition, easy-to-obtain markers such as NLR, PLR and LMR have been shown to be clinically useful in the early postoperative period [206]. Furthermore, the T-cell CD69 ratio combined with PCT can accurately differentiate between gram-negative and gram-positive sepsis and also has predictive value [207].

The range of biomarkers is constantly increasing based also on multi-omics and non-coding RNA research. Excessive expression of CEACAM8, MPO and RETN has been demonstrated to be closely correlated with disease progression, hence offering potential as diagnostic urinary biomarkers [208]. In addition, the correlation between PGK1 and immune cell infiltration and inflammation regulation also demonstrates its potential as a new diagnostic index [209]. Furthermore, the roles of ncRNAs have become a subject of much interest. LINC01278 serves as a sponge of miR-451a to weaken inflammation and organ injury, and MEG3 rs7158663 GG genotype dramatically elevates genetic susceptibility and adverse outcome risk through promoting the overflow of inflammatory factors [210, 211]. Together, these findings depict a multidimensional biomarker network encompassing metabolic, genetic, immune, and non-coding RNA pathways. This network not only deepens our understanding of the complex molecular landscape of sepsis but also facilitates improved patient stratification and immune status monitoring. Importantly, these advances provide a critical basis for the development of precision medicine approaches and targeted therapeutic strategies, paving the way for the emerging immunomodulatory and adjunctive therapies discussed in the following section.

## 6 EMERGING THERAPEUTIC STRATEGIES AND CLINICAL CHALLENGES

### 6.1 Targeted immunomodulatory therapies

Recently, the investigation of therapeutic immune modulation has become a major trend in sepsis research. Promising approaches such as small molecules and targeted agents were discussed. For example, PLX5622 prevents neuronal injury and synapse loss by suppressing microglial activation, attenuating SAE [212]. However, the PSMA4-associated protein degrader has been identified as a new target for therapy and may reduce the risk of sepsis development [213]. Among traditional pharmacological strategies, glucocorticoids in combination with fludrocortisone have been evaluated in a component network meta-analysis of 33 randomized controlled trials including 9,898 patients, in which this combination was associated with reduced short-term mortality (RR 0.89) and improved long-term mortality in adults with sepsis and septic shock, highlighting their potential as an adjunctive therapy [214]. In addition, a prospective multicenter study of granulocyte–monocyte adsorption apheresis in 82 patients with sepsis demonstrated a significant reduction in SOFA score at 7 days and a 28-day mortality rate of 7.8%, supporting its safety and potential adjunctive benefit [215].

Moreover, the profiling of immune-cell functions has also identified additional possibilities for therapeutic intervention. Single-cell immune profiling further demonstrates the heterogeneity of immune cells in PICS post-sepsis, which offers

potential individual targets for risk evaluation and precision treatment [216]. At the molecular pathway level, caspase-11/GSDMD was found to regulate NET generation via neutrophil activation, which indicates GSDMD may be a therapeutic target for sepsis treatment [217]. By contrast, HMGB1 can act as a ligand for Tim-3 to elicit immunosuppression via inhibition of NF-κB signaling in $CD4^+$ T cells, thus representing a potential translational impact [218]. Metabolism-regulating molecules like NLRC3 mediate immunosuppression by shaping macrophage metabolism, and the targeted intervention can possibly restore the immune derangement during sepsis [219]. A $CXCR2^+$ neutrophil subset has been demonstrated to promote pulmonary immune dysregulation, and its blockade could help in mitigating lung injury and improving outcomes [157]. Furthermore, ulinastatin also exerts unique immunomodulatory effects through dual regulation of neutrophils and MDSCs [220].

Platelets, T cells and metabolic pathways have also been identified as potential therapeutic targets. Platelets modulate the function of $CD8^+$ T cells through MHC-I-mediated cross-presentation of antigens, and this newly described mechanism offers new opportunities in immunotherapeutic approaches [158]. IFN-γ can also restore immunosuppression by promoting a switch to the Warburg effect through the PI3K/Akt/mTOR pathway, and Inducible T-cell Co-Stimulator (ICOS)-Fc bimodulates the ICOS–ICOSL signaling axis, significantly ameliorating systemic inflammatory response syndrome and multiple organ injuries [221, 222]. Interventions on cellular and molecular levels still increase. Hematopoietic stem cell infusion, for instance, can increase MDSCs and suppress inflammation to improve survival; low-dose esmolol attenuates T cell apoptosis and normalizes Th1/Th2 imbalance by acting on the Akt/Bcl-2/Caspase-3 and ERK1/2 pathways [223, 224].

Promising microorganism and non-coding RNA-mediated therapies are also emerging. Tripeptide Arginine-Lysine-Histidine (RKH), derived from Akkermansia muciniphila (AKK), reduces inflammation and organ damage by inhibiting TLR4 signaling [66]. Nicorandil alleviates myocardial injury through mediating ferroptosis of the TLR4/SLC7A11 pathway; low-dose mycophenolate mofetil reinforces anti-bacterial activity of macrophage, hence promoting bacterial clearance for survivors [225, 226]. Molecularly, miR-150 supplementation can reverse the immunosuppressive role of MDSCs as an innovative intervention strategy for late-stage sepsis; additionally, in preclinical caecal ligation and puncture (CLP) models, umbilical cord–derived MSCs and their conditioned media were shown to mitigate organ injury, enhance bacterial clearance, reduce serum lactate and pro-inflammatory cytokine levels, and improve survival when administered within a defined therapeutic window [227, 228].

The paradigm of sepsis immunoregulation is shifting from single-target interventions toward systemic reprogramming strategies. Emerging evidence indicates that sepsis induces metabolic reprogramming and dysregulated IL-17 production in $CD4^+$ T cells, leading to persistent immune dysfunction and impaired host defense after recovery [9]. These findings highlight the critical role of immunometabolic imbalance in sepsis pathophysiology and have stimulated increasing interest in therapeutic strategies targeting immune and metabolic dysregulation.

Within this evolving framework, diverse therapeutic approaches converge on a common objective: restoring immune homeostasis and cellular energy balance. Current strategies include cell-based therapies, nanodelivery systems, metabolic reprogramming, and targeted immunomodulation (see **Table 3**), reflecting a growing trend toward multi-target and system-level interventions. For example, mitochondrial transplantation has been shown to reverse sepsis-induced metabolic suppression and restore immune cell bioenergetics, promoting recovery of oxidative metabolism and biosynthetic capacity [253]. Beyond metabolic modulation, therapeutic strategies targeting inflammatory responses and oxidative stress are also emerging as promising approaches in sepsis management.

### 6.2 Novel approaches in antioxidant and anti-inflammatory therapy

In recent years, different therapeutic options for sepsis have emerged, and several promising new strategies have appeared with great clinical potential. Plasma exchange has been evaluated in a meta-analysis of five controlled trials, in which it was associated with reduced all-cause mortality in adults with severe sepsis (OR 0.54), although heterogeneity among studies was substantial and larger randomized trials are still required to confirm these findings [254]. Early enteral nutrition has emerged as a promising and generally safe therapeutic strategy in critically ill patients with sepsis and septic shock. A systematic review including five randomized controlled trials (n=442) and ten non-randomized studies (n=3,724) suggested that early enteral nutrition was associated with fewer days of mechanical ventilation and lower SOFA scores during follow-up, although no statistically significant reduction in in-hospital mortality was observed [255]. The immunomodulator glatiramer acetate (GA) has demonstrated anti-inflammatory and immunomodulatory effects in a CLP murine model of sepsis. Acute administration (1–2 mg/kg) significantly improved 72-hour survival and reduced pro-inflammatory cytokine levels, suggesting potential therapeutic relevance that warrants further clinical investigation [256].

In anti-infective therapy, the combination of azithromycin with exosomes provides a new therapeutic agent for sepsis by boosting infection clearing and regulating inflammation [257]. Nutmeg extract attenuates platelet desialylation and clearance by suppressing sepsis-elicited sialidase activity, indicating its prospect for use in the treatment of sepsis and sepsis-associated

**Table 3. Innovative intervention strategies and their research progress**

| Intervention type | Representative drug/method | Mechanistic target | Clinical progress/trial stage | Limitations | References |
|---|---|---|---|---|---|
| Cell therapy | Autologous neutrophils subjected to cryo-shock | Broad-spectrum neutralization of inflammatory cytokines and endotoxins | Preclinical study | Further clinical validation required for efficacy and safety | [229] |
| Nanomedicine | NAD(H)-loaded nanoparticles | Supplementation of NAD(H) to enhance energy supply and suppress inflammation | Preclinical study | Biosafety of nanomaterials and their clinical translational potential require validation | [230] |
| Immunometabolic modulator | MSM | Promotes macrophage M2 polarization via the lactate-H3K18la pathway | Preclinical study | Mechanistic insights require further elucidation, and clinical efficacy remains to be validated | [231] |
| Metabolites | FMT and SCFAs | Modulates gut microbiota, inhibits pyroptosis, and protects intestinal barrier | Preclinical study | Safety and efficacy in humans require clinical validation | [232] |
| Immune checkpoint inhibitor | Nivolumab combined with meropenem | Inhibits the PD-1 pathway and reverses T cell exhaustion | Mathematical modeling simulations; preclinical stage | Efficacy depends on precision medicine; ineffective under high pathogen load | [233] |
| Blood purification | CVVH | Removes inflammatory mediators and improves immune and endothelial function | Small randomized controlled trial | Did not reduce 28-day mortality or shorten hospital stay | [234] |
| Stem cell therapy | MSCs and their exosomes | Targets the MALAT1 pathway via delivery of miR-26a-5p | Preclinical study | Mechanism is complex; clinical safety and efficacy require validation | [235] |
| Immunomodulatory therapy | C1q-blocking antibody and PLX5622 | Inhibits C1q-mediated synaptic pruning and microglial activation | Preclinical study | Clinical validation has not been conducted; efficacy remains to be evaluated | [212] |
| Complement system targeting | C5a receptor 1 (C5ar1) gene deficiency | Blocks C5ar1 to reverse immunosuppression | Preclinical study | Based on gene deficiency models; drug development and efficacy require validation | [236] |
| Novel small-molecule drug | Songorine | Activates the Nrf2/ARE pathway to promote mitochondrial biogenesis | Preclinical study | Plant-derived compound; clinical translational potential remains to be validated | [237] |
| Herbal medicine | Rhodiola rosea extract | Inhibits the PI3K-AKT pathway to alleviate inflammation and oxidative stress | Preclinical study | Complex composition; mechanism requires further elucidation, and clinical efficacy remains to be validated | [238] |
| Drug repurposing | Montelukast | Inhibits downstream inflammatory and oxidative stress pathways such as LTB-4 | Preclinical study | Currently at the animal experiment stage; clinical efficacy is unknown | [239] |
| Natural product | Isoflavone osajin | Inhibits the IL-33/LPO/8-OHdG/caspase-3 pathway | Preclinical study | At the animal experiment stage; clinical efficacy remains to be validated | [240] |
| Protein-delivery nanomedicine | MF-LNP encapsulating SOD/CAT | Efficiently delivers antioxidant enzymes to scavenge ROS | Preclinical study | Safety and clinical translational potential of the novel delivery system require validation | [241] |
| Therapeutic strategies targeting METTL3 | METTL3 inhibitors or knockdown approaches | Inhibits METTL3 to block $m^6A$-dependent ferroptosis | Preclinical study | Clinical validation has not been conducted; safety and efficacy remain to be evaluated | [242] |
| Drug repurposing | Dexmedetomidine | Activates astrocytic α2A adrenergic receptors | Preclinical study | Mechanism requires further elucidation; clinical efficacy remains to be validated | [110] |
| Probiotic-derived peptides | AKK or its derived tripeptide RKH | Acts as an endogenous TLR4 antagonist to block TLR4 Signaling | Preclinical study | Human trials have not been conducted; clinical translational efficacy remains to be validated | [66] |

| | | | | | |
|---|---|---|---|---|---|
| Microbial therapy | Lactobacillus rhamnosus GG | Modulates gut microbiota and reduces systemic inflammation via macrophages | Preclinical study | Mechanism is indirect, no direct effect on the brain; clinical efficacy remains to be validated | [243] |
| Herbal medicine | Gedunin | Inhibits the HMGβ1/NLRP3/NF-κB signaling pathway | Preclinical study | At the animal experiment stage; clinical translational potential remains to be validated | [244] |
| Monoclonal antibody | Humanized anti-citrullinated histone H3 monoclonal antibody | Blocks the CitH3-TLR2 signaling axis to inhibit NETosis and pyroptosis | Preclinical study | Has not entered clinical trials; safety and efficacy remain to be validated | [245] |
| Uridine supplementation therapy | Uridine as a metabolic supplement | Activates the Nrf2 signaling pathway to inhibit macrophage ferroptosis | Preclinical study | At the animal experiment stage; clinical translational potential remains to be validated | [246] |
| Targeted immunomodulation | Disulfiram or GSDMD gene knockout | GSDMD/caspase-11 pathway | Preclinical study | At the animal experiment stage; clinical efficacy remains to be validated | [217] |
| Neuroimmune modulation | Electroacupuncture | Promotes M2 macrophage polarization by upregulating spermidine and ODC expression | Preclinical study | At the animal experiment stage; clinical translational potential remains to be validated | [247] |
| Physical therapy | Nurse-led, goal-oriented pulmonary physical therapy | Improves pulmonary ventilation and drainage via physical means; no clear molecular target | Completed clinical controlled studies showing improvement in clinical outcomes | Implementation depends on a specialized nursing team | [248] |
| Photodynamic therapy | Aloe-emodin-mediated photodynamic therapy | Inhibits the expression and activity of gram-positive bacterial toxins such as cytolysins, hemolysins, and pneumolysins | Preclinical study | Clinical efficacy remains to be validated | [249] |
| Gut microbiota modulation | Metformin | Modulates gut microbiota and alleviates colonic barrier dysfunction | Preclinical study | At the animal experiment stage; clinical translational potential remains to be validated | [250] |
| Protein supplementation | Vitamin D binding protein | Alleviates oxidative stress and inhibits the JNK signaling pathway | Preclinical study | Mechanism requires further elucidation; clinical efficacy remains to be validated | [83] |
| High-dose antioxidant therapy | High-dose intravenous vitamin C | Antioxidant effect (specific molecular target not clearly defined) | Ongoing multicenter randomized phase III clinical trial | Trial is ongoing; efficacy and safety outcomes are unknown | [93] |
| Natural product | Curcumin | Reduces free radicals, enhances antioxidant enzymes, and inhibits iNOS | Preclinical study | At the animal experiment stage; clinical efficacy remains to be validated | [251] |
| Kinase inhibition | Fgr kinase inhibitor | Fgr kinase → SIRT1/PGC-1α signaling pathway | Preclinical study | At the animal experiment stage; clinical efficacy remains to be validated | [252] |

thrombocytopenia [258]. In addition, oXiris continuous hemofiltration adsorption was evaluated in a retrospective cohort of 90 patients with sepsis or septic shock. Significant improvements in hemodynamic parameters, lactate levels, inflammatory biomarkers (procalcitonin and IL-6), and SOFA scores were observed at 12 and 24 hours post-treatment. Pre-treatment SOFA score, percentage SOFA reduction, and age were identified as independent predictors of ICU mortality. Although these findings suggest potential benefits in organ function stabilization, prospective randomized trials are needed to confirm survival impact [259].

Recently, immunomodulatory therapy has become an innovative approach to the treatment of sepsis. For instance, hPF4 complexes with cfDNA and NETs to suppress thrombosis and endothelial injury, which could be potential targets for immune therapy in sepsis [260]. Codonopsis Pilosula Extract reduces immune organ damage in septic rats, and keeps the immune homeostasis by regulating BCR signaling pathway and glycerophospholipid metabolism, highlighting its future potential for sepsis immunomodulation [261]. For sepsis-related lung injury, montelukast mitigates lung tissue damage, and its administration effectively ameliorates the polymicrobial sep-

sis-induced increase in inflammatory mediators and oxidative stress, thereby providing protection [239]. Gedunin exhibits a marked protective effect against oxidative stress and inflammation by suppression of HMGB1/NLRP3/NF-κB signaling pathway in septic mouse models, which provides valuable implications for its promising therapeutic applications [244]. Songorine can act through Nrf2/ARE and Nrf1 signaling pathways to enhance mitochondrial biogenesis, ameliorate cardiac function, and provide protective effects against sepsis-induced myocardial injury [237].

In the treatment of kidney injury, Osajin mitigates sepsis-induced acute kidney injury (SI-AKI) by suppressing the IL-33/Lipid Peroxidation (LPO)/8-hydroxy-2'deoxyguanosine (8-OHdG)/caspase-3 pathway and promoting antioxidant defense, indicating its possible use in sepsis therapy [240]. The deletion of MALAT1 controls epigenetic regulation, activates the methionine cycle, and improves antioxidative activity, which may provide a new direction for the treatment of sepsis [262]. Moreover, betaine remarkably decreases the levels of inflammatory and oxidative stress markers, improves gas exchange and imaging findings as well as protective effects against sepsis-induced ARDS [263].

Regarding cardiac preservation, the Mitochondria-targeted 2,2,6,6-tetramethylpiperidine-1-oxyl (MitoTEMPO) enhances mitochondrial biogenesis and protects against sepsis-induced renal injury by decreasing mROS and IL-1β [264]. MSCs and their exosomal miR-26a-5p delivery target and suppress MALAT1 to alleviate hepatocyte death and oxidative stress, and are protective against sepsis-induced ALI [235]. Furthermore, matairesinol is a potent neuroprotectant against sepsis-induced brain damage by activating the AMPK/Nrf2 signaling pathway and blocking MAPK/NF-κB pathways to reduce both neuroinflammation and oxidative stress [265].

In terms of neuroprotection, quercetin also markedly mitigates SAE through the suppression of the CXCL2/CXCR2 axis, associated microglial activation, and neuronal ferroptosis [266]. Eriocitrin protects against SA-AKI through the activation of Nrf2 pathway, mitochondrial dynamics, and decrease in inflammation and oxidative stress [267]. Taohe Chengqi Decoction can effectively suppress the inflammatory response and correct immune imbalance in sepsis via mediation of several signaling pathways, such as MAPK and STAT3, thereby representing a potential therapeutic strategy for sepsis [268].

Emerging immunomodulatory and antioxidant therapeutic strategies have shown great potential in the clinical management of sepsis, particularly in improving patient outcomes. Further elucidating these therapeutic mechanisms and advancing their clinical translation will pave the way for personalized treatment and precise interventions in sepsis.

### 6.3 Application of personalized medicine in sepsis

Innovative sepsis management approaches have increasingly demonstrated the intimate interplay of patients' immune responses, metabolic alterations and clinical outcome. Dynamic fluid monitoring is one of the most efficient methods for improving the prognosis of patients with septic shock [269]. In addition, enhanced external inspection and monitoring could shorten antibiotic therapy and fluid resuscitation durations effectively to optimize the clinical treatment program significantly [270]. Furthermore, the low expression of miR-146b-5p in patients with sepsis is closely related to a poor prognosis. When the APACHE II score is used in conjunction, it greatly increases the accuracy of the diagnosis. Similarly, tracking the dynamics of lymphocyte subsets strongly advocates for individualized treatment [271]. Immune heterogeneity of sepsis has been demonstrated by SRS molecular typing. This result offers an important theoretical basis for precision medicine, and indicates that personalized treatment guided by the host immune response status may be the direction for improving sepsis prognosis [7].

To better stratify sepsis, studies using coagulation biomarkers have identified four distinct sepsis phenotypes. Among these phenotypes, patients with high fibrin degradation products/D-dimer levels may be more responsive to thrombomodulin therapy, supporting the development of personalized medicine approaches for sepsis [272]. The underlying mechanisms of immune diversity have also been further revealed by studies highlighting dysregulation of the R/SI balance, offering a potential strategy for classifying patients based on immune status and matching them with specific therapies [273]. Although metagenomic next-generation sequencing can rapidly identify pathogens in patients with sepsis, its use in guiding antibiotic adjustment has not significantly improved patient prognosis. This suggests that pathogen identification should be better integrated with clinical diagnosis and treatment decision-making [274]. Results from a large statewide cohort study involving over 55,000 patients demonstrated that timely completion of the 3-hour sepsis bundle was associated with reduced risk-adjusted in-hospital mortality, with a more pronounced effect observed in the δ subtype [275]. These studies also highlight metabolic disruption of critical pathways during sepsis, which not only offers new targets for intervention but also promotes precision medicine in sepsis management through multidisciplinary approaches [276]. Studies of sepsis-associated acute kidney injury (SA-AKI) have identified microcirculatory dysfunction, inflammasome activation, and metabolic reprogramming as important pathogenic elements, thereby providing a basis for molecular target-based therapies [277].

In the chronic phase of sepsis, gut microbiota dysbiosis may persist for 14–21 days after onset. Notably, sex-specific differences have been observed, with females exhibiting greater

resilience than males. This observation may open up a unique point for microbiota-based intervention in sepsis [278]. Meanwhile, single-cell sequencing disclosed an atypical lymphocytic transcriptional signature in late sepsis characterized by the concomitance of immunoparalysis and micro-inflammation. This offers new possible applications for precision immunotherapy [279]. Early use of norepinephrine in septic shock can rapidly increase and stabilize arterial blood pressure, and may help limit prolonged hypotension and fluid overload. Observational studies, including propensity score-based analyses, have reported reduced fluid administration and inconsistent effects on day-28 mortality with early norepinephrine initiation, whereas a randomized controlled trial using fixed-dose norepinephrine (0.05 μg/kg/min) demonstrated improved shock control without a confirmed survival benefit, suggesting outcome heterogeneity across patient subgroups [280]. Detailed studies on the accurate classification of sepsis have shown that SR-BI deficiency is associated with sepsis of the relative adrenal insufficiency subtype, a chronic subgroup with sustained excessive inflammation. These studies also show that glucocorticoids are effective for this subtype, highlighting the importance of bundle therapy in sepsis [281]. Furthermore, the combination of IL-10 and the NEWS score provides important biomarker support for early sepsis stratification by identifying patients with low clinical scores and high physiological risk, offering a new avenue for clinical prognostic evaluation [204].

Unique medical approaches to sepsis are emerging through accurate immune profiling, metabolic monitoring, and mechanistic research, which facilitate early identification, risk stratification, and individualized therapy. Detailed characterization of host immune responses and metabolic disturbances provides new opportunities for precision treatment and improved patient outcomes. However, translating these advances into routine clinical practice remains challenging due to the complexity and heterogeneity of sepsis, which highlights the need for further investigation and clinical validation.

## 7 DISCUSSION

Despite substantial advances in sepsis research over the past decades, its clinical translation remains challenging. The pathophysiology of sepsis is highly complex, making it difficult for single-target therapies to maintain sustained therapeutic efficacy. One major reason is the dynamic biphasic nature of the immune response during sepsis. In the early hyperinflammatory phase, Tregs help limit excessive inflammation and reduce tissue damage. However, during the subsequent immunosuppressive phase, the expansion of Tregs may further suppress effector immune responses, thereby exacerbating immunosuppression and contributing to poor clinical outcomes [282]. Consequently, conventional anti-inflammatory therapies often overlook this stage-dependent immune regulation, making the timing, intensity, and duration of intervention critical determinants of therapeutic efficacy. For example, inhibitors targeting TLR4 demonstrated promising early efficacy in experimental models but failed to improve outcomes in clinical trials, highlighting the importance of appropriate therapeutic timing and immune status assessment. In addition, innate immune signaling pathways exhibit complex regulatory roles in sepsis. Although sepsis drives persistent platelet activation and dysfunction, TLR7 deficiency has been shown to preserve platelet function and modulate exosome-mediated platelet activation, suggesting that TLR7 may represent a key regulator of sepsis-associated platelet dysfunction and a potential therapeutic target [283].

Moreover, the marked heterogeneity of sepsis represents another major obstacle to precision medicine. Immune responses in sepsis are shaped by multiple endogenous and exogenous factors, including genetic background, age, sex, comorbidities, metabolic status, prior microbial exposure, and pharmacological interventions [284]. Multi-omics analysis indicates that immune-metabolic subtypes, including glycolysis-dominant and oxidative types, may underlie differential responses to treatment. Accordingly, future clinical studies should employ personalized interventions according to molecular subtypes, rather than a uniform strategy [285]. The interaction between inflammation and metabolic networks still requires more systematic analysis. Mitochondrial dysfunction, ferroptosis, and NLRP3 inflammasome activation represent common nodes in organ damage, but their timing and tissue specificity have yet to be fully elucidated [286]. By integrating metabolomics, spatial transcriptomics, and single-cell immune profiling, it is expected to uncover organ-specific pathological pathways, enabling more precise intervention design.

With respect to the treatment, several new immunomodulatory and antioxidant treatments have provided promising results. Targeting multiple aspects of these pathways has been observed to enhance treatment responsiveness in systemic models, leading to improved survival rates. Examples of such approaches include autophagy enhancement, Nrf2 activation, and pyroptosis inhibition (e.g., rapamycin, MitoTEMPO, and songorine), indicating the potential for multi-pronged therapeutic strategies [129]. Meanwhile, the application of exosomes from stem cells, non-coding RNAs, and gut microbiota regulation is uncovering new avenues for systemic immune reconstitution. When integrated with AI-predictive models and real-time biomarker feedback in the future, digital twin models may become increasingly feasible.

Interdisciplinary integration is likely to be a major direction in future sepsis research. The integration of immunology, metabolomics, systems biology and AI will enable a comprehensive understanding of the “pathogen-to-host network”. Through developing interpretable immune-metabolic-genetic multi-dimensional models, it will not only reveal the mechanisms underlying individual susceptibility but also guide clini-

cal practice toward precise, dynamic, and reproducible personalized interventions.

## ABBREVIATIONS

8-OHdG, 8-Hydroxy-2'-deoxyguanosine; AKI, Acute kidney injury; AKK, Akkermansia muciniphila; ALI, Acute lung injury; Ang-2, Angiopoietin-2; AQP3, Aquaporin-3; ARDS, Acute Respiratory Distress Syndrome; BM, Bone marrow; C5ar1, C5a receptor 1; CETP, Cholesteryl Ester Transfer Protein; CLP, Cecal ligation and puncture; DNMT, DNA methyltransferase; EIF2AK2, Eukaryotic translation initiation factor 2α kinase 2; ERK, Extracellular Signal-Regulated Kinase; GA, Glatiramer acetate; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; GPR, G protein-coupled receptors; GPX4, Glutathione Peroxidase 4; GSDMD, Gasdermin D; H3K14la, Histone H3 lysine 14 lactylation; HDAC, Histone Deacetylase; HDL, High-Density Lipoprotein; HLA, Human Leukocyte Antigen; HLH, Hemophagocytic lymphohistiocytosis; HLJ1, Heat shock protein 40-like protein 1; HMGB1, High mobility group box 1; ICOS, Inducible T-cell Co-Stimulator; LNP, Lipid nanoparticles; LPIN1, Lipin 1; LPO, Lipid Peroxidation; LPS, Lipopolysaccharide; LqSOFA, Liverpool quick Sequential Organ Failure Assessment; $m^6A$, N6-methyladenosine; MALAT1, Metastasis-Associated Lung Adenocarcinoma Transcript 1; MCP-1, Monocyte Chemoattractant Protein-1; MDSCs, Myeloid-derived suppressor cells; METTL, Methyltransferase-Like; MHC, Major histocompatibility complex; MitoTEMPO, Mitochondria-targeted 2,2,6,6-tetramethylpiperidine-1-oxyl; MMP, Matrix metalloproteinase; MSCs, Mesenchymal stem cells; MyD88, Myeloid differentiation primary response 88; NETosis, Neutrophil Extracellular Trap formation; NETs, Neutrophil extracellular traps; NEWS, National Early Warning Score; NLRs, NOD-like receptors; NOP, Nociceptin/Orphanin FQ receptor; Nrf2, Nuclear factor erythroid 2–related factor 2; OLFM4, Olfactomedin 4; PAD4, Peptidylarginine Deiminase 4; PADI, Peptidyl Arginine Deiminase; PAI-1, Plasminogen Activator Inhibitor-1; PANX1, Pannexin 1; PGC-1α, Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha; PICS, Persistent Inflammation, Immunosuppression, and Catabolism Syndrome; PINK1, PTEN-induced kinase 1; PKM, Pyruvate Kinase, Muscle; PMN, Polymorphonuclear Myeloid; PRRs, Pattern recognition receptors; RANTES, Regulated upon Activation, Normal T Cell Expressed and Secreted; RKH, Tripeptide Arginine-Lysine-Histidine; ROCK, Rho-associated coiled-coil containing protein kinase; ROS, Reactive Oxygen Species; S1P, Sphingosine-1-phosphate; SAA, Serum amyloid A; SA-AKI, Sepsis-Associated acute kidney injury; SI-AKI, Sepsis-induced acute kidney injury; SAE, Sepsis-associated encephalopathy; Skp2, S-phase kinase-associated protein 2; SLC3A2, Solute Carrier Family 3 Member 2; SOFA, Sequential Organ Failure Assessment; SphK1, Sphingosine kinase 1; SRS, Sepsis Response Signature; SuPAR, Soluble urokinase-type plasminogen activator receptor; Tim-3, T-cell immunoglobulin and mucin domain-containing protein 3; TLRs, Toll-like receptors; TSLP, Thymic stromal lymphopoietin; VDAC2, Voltage-Dependent Anion Channel 2; VEGF, Vascular Endothelial Growth Factor; VISTA, V-domain Immunoglobulin Suppressor of T-cell Activation.

## DECLARATIONS

### Author contributions

Xuesong Liu, Jiejin Yang, and Zhihao Hu contributed equally to this work and share first authorship. Xuesong Liu, Jiejin Yang, and Zhihao Hu were responsible for conceptualization, literature investigation, and writing the original draft. Huiting Wei and Rong Zhang contributed to validation and formal analysis. Zhuoqun Huang performed visualization and prepared the figures and tables. Jiao Song supervised the project and provided critical revisions for important intellectual content, and served as the corresponding author. All authors have read and approved the final manuscript.

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### Competing interests

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