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REVIEW ARTICLE

Unveiling the complex network of sepsis and cytokine storms: New perspectives from mechanisms to interventions

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Abstract

Sepsis is a systemic inflammatory response syndrome triggered by infection. It presents with simultaneous overactive immune activation and immune paralysis, leading to a cytokine storm, tissue injury, and multiple organ failure. The molecular mechanisms and pathological characteristics of the septic cytokine storm are comprehensively interpreted from multiple perspectives, including immune regulation, signaling pathways, cellular interactions, metabolic state reprogramming, and microcirculatory dysfunction. The cross-activation of signaling pathways, including NF-κB, JAK/STAT, mitogen-activated protein kinase (MAPK), and NLRP3 inflammasome, underlies the core mechanism for the enhancement of the inflammatory response via continued release of pro-inflammatory cytokines and also is involved in maintaining immune balance. In the late-stage immunosuppressive phase, Treg cells, myeloid-derived suppressor cells (MDSCs) and regulatory macrophages play pivotal roles in reestablishing host homeostasis through negative feedback, and their dysfunction is closely associated with secondary infections and high mortality. This review consolidates the latest developments in precision medicine and multidimensional biomarkers, emphasizing the prospective value of several markers such as lactate and CD64, pentraxin 3 (PTX3), and BMP9 for early diagnosis and prognosis evaluation. Moreover, it reviews novel immunomodulators, for instance, bee venom peptides, GDF15, N-(1,3,4-oxadiazol-2-yl) guanidine (NWG), 4-octyl itaconate (4-OI), and nanoparticle drug delivery systems that inhibit inflammatory signaling cascades, restore energy metabolism, and provide organ protection. Taken together, the pathogenic mechanisms of sepsis are non-linear and dynamic, which may render single-target therapy insufficient for successful management. Personalized interventions targeting multi-target network regulation based on omics and AI models may accomplish precision monitoring and stratified treatment of inflammatory responses, also providing new theoretical and clinical strategies to reduce sepsis-related mortality.

Keywords: Sepsis, Cytokine storm, Immune regulation, Metabolic reprogramming, NLRP3 inflammasome, Precision medicine, Biomarkers, Immune suppression

1 INTRODUCTION

Sepsis is an infection-induced systemic inflammatory response syndrome. Overactivation of the immune system during its progression results not only in hyper-inflammatory responses but may also be associated with immunosuppression, known as immune paralysis, which makes treatment difficult. However, therapies to decrease immune activation may have deleterious

effects on patients who are immunoparalyzed due to viral infection or sepsis [1]. Clinically, sepsis still has a high incidence and mortality, and remains a major public health problem worldwide. In 2017, the global number of new sepsis cases was estimated at 48.9 million (95% UI: 38.9–62.9), with an estimated 11 million sepsis-related deaths (95% UI: 10.1–12.0) [2]. The challenging development of existing therapies and their limited benefits underscore the pressing need for early diagnosis and targeted treatments. Among these, the cytokine storm is the most important characteristic of sepsis. It refers to an overwhelming shift toward pro-inflammatory responses over anti-inflammatory responses, resulting in systemic inflammatory amplification and immune homeostasis. High levels of serum ferritin were closely associated with increased formation of neutrophil extracellular traps (NETs) and aggravation of lung injury in sepsis patients, suggesting that ferritin might become a significant marker for assessing inflammation severity and immune imbalance. There is evidence that its level is closely associated with overall prognosis in sepsis patients [3].

Although therapeutic strategies for sepsis have greatly improved and may include antimicrobial therapy, fluid resuscitation, and supportive organ therapy in clinical practice, single-target intervention is not compatible with the complex supernetwork exhibited by the cytokine storm. The intercellular signaling pathways in sepsis represent a coordinated immunometabolic cross-talk. Studies have demonstrated that hepatocyte mitochondria are metabolically linked to TREM2-expressing liver macrophages, and disruption of this coordination may be further amplified during inflammatory responses and organ damage. This indicates that intercellular metabolic communication may represent a novel point of entry for precision interventions [4]. Additionally, GABA regulation, metabolic reprogramming, and the inflammatory macrophage response mediated by protein succinylation are also implicated, which complicates the non-linear dynamics of the pathophysiological mechanisms in sepsis. This complexity explains why the therapies developed so far have such narrow application ranges. Furthermore, the crosstalk within the inflammatory network, negative feedback regulation, and immune suppression in late-phase sepsis induce a transition from excessive inflammation to an immunodeficiency state, which predisposes patients to secondary infections and death. This also implies that early in the course of treatment, blood cultures probably have poor sensitivity for diagnosing patients with severe sepsis, especially if empirical antimicrobial therapy has been initiated [5].

In light of the above background, a systematic study of the multi-center network mechanisms in the sepsis cytokine storm, as well as immune regulation features and possible intervention strategies, has important theoretical and clinical implications. This review summarizes the main pathological mechanisms of sepsis, such as hyperimmune activation, the inflammatory cytokine network, cell communication disturbances in the microcirculation, metabolic reprogramming, and multiple modalities of cell death, and discusses immune regulation and negative feedback mechanisms that maintain host homeostasis. In addition, the review also discusses recent progress in precision medicine, biomarkers, and novel immunomodulators to establish a theoretical basis for multi-targeted and controllable intervention strategies.

2 MOLECULAR MECHANISMS OF THE CYTOKINE STORM

2.1 Overactivation and dysregulation of the immune system

The pathologic immune response in sepsis, commonly referred to as a "cytokine storm", reflects a profound imbalance between innate and adaptive immunity [6]. During early infection, macrophages, dendritic cells, and neutrophils are activated through pattern recognition receptors, including Toll-like receptors (TLRs), NOD-like receptors, and RIG-I-like helicases, leading to activation of central inflammatory signaling pathways such as NF-κB, MAPK, and JAK/STAT [7, 8]. Rather than reiterating their canonical cascades here, it should be noted that in sepsis these pathways become persistently amplified, driving excessive production of TNF-α, IL-1β, IL-6, IL-8, and IFN-γ and forming self-reinforcing inflammatory loops that culminate in tissue injury. The synergistic effect of TNF-α and IFN-γ can induce lethal cytokine shock, whereas inhibition of PANoptosis alleviates tissue damage and improves survival [8]. In addition, NONO enhances extracellular signal-regulated kinase (ERK)1/2 activation and cytokine release, while aberrant NLRP3 inflammasome activation serves as a pivotal amplification node contributing to sustained inflammation and multiple organ dysfunction syndrome (MODS) [6].

Excessive innate immune activation further promotes neutrophil extravasation and endothelial cell injury. Elevated ferritin can induce systemic inflammation in a macrophage scavenger receptor-dependent manner and promote NET formation through the coordinated activity of PAD4, neutrophil elastase, and reactive oxygen species, thereby aggravating acute lung injury (ALI) and microcirculatory dysfunction [3, 9]. Direct endothelial cell–neutrophil interaction also enhances NET generation, and the adhesion molecule macrophage-1 antigen (Mac-1) has emerged as a potential therapeutic target for mitigating NET-associated inflammation [9].

Adaptive immune dysfunction likewise contributes to both hyperinflammation and subsequent immune paralysis. The ATP–P2X purinoceptor 7 pathway regulates liver pannexin 1–IL-33 immune homeostasis, and exogenous IL-33 promotes $ST2^+$ regulatory T cell (Treg) expansion, reducing cytokine storm severity and improving survival in sepsis models. GPR174-deficient Tregs facilitate macrophage repolarization toward the anti-inflammatory M2 phenotype and suppress IL-6

and TNF-α production [10]. Conversely, IL-1R2$^+$ monocytes/macrophages generated by granulocyte-macrophage colony-stimulating factor (GM-CSF) and lipopolysaccharide (LPS) exhibit reduced HLA-DR expression and upregulation of immunosuppressive markers such as MS4A4A and CD63, representing a sepsis-like immunoparalytic phenotype [11].

Under chronic inflammatory conditions, the indoleamine 2,3-dioxygenase 1 (IDO1)-AHR- CYP1A1 axis forms a positive feedback loop with canonical cytokine signaling pathways, further amplifying inflammatory responses; this process can be attenuated by IDO1 inhibition [12]. Meanwhile, myeloid differentiation primary response 88 (MyD88)-dependent signaling in myeloid cells and cardiomyocytes contributes to endotoxin shock-induced systemic inflammation and cardiac dysfunction. Collectively, immune dysregulation in sepsis arises from integrated processes of pathogen sensing, signaling amplification, metabolic imbalance, and impaired immune regulation, leading not only to organ damage but also to both immune paralysis and secondary infections.

2.2 Inflammatory cytokine networks and signaling pathways

The cytokine storm is caused by the excessive release of several pro-inflammatory cytokines [13, 14]. A characteristic of this storm is the dynamic imbalance between the innate and adaptive immune responses, resulting in dysregulated systemic inflammation. In the context of sepsis and its accompanying ALI, the induction of this inflammatory cytokine network exhibits dynamic, non-linear amplification properties [13]. Several driving cytokines/chemokines such as TNF-α, IL-1β, IL-6, IFN-γ, IL-8, GM-CSF, and MCP-1 establish a positive feed-forward loop by cross-activating multiple signal transduction pathways, thereby aggravating tissue injury [13, 14].

Molecularly, the NF-κB, JAK/STAT, MAPK, and NLRP3 inflammasome pathways are the central nodes governing the cytokine storm [15]. In addition, Huashi Baidu Decoction inhibits the cytokine storm by modulating the TLR4/NF-κB and PI3K/Akt signaling pathways [13]. On the other hand, COB-187 suppresses inflammatory cascades by attenuating the DNA-binding activity of NF-κB (p65/p50) and the phosphorylation of IRF-3 at Ser396. Additionally, the JAK/STAT signaling pathway amplifies inflammation by regulating secondary cytokine production via IFN and IL-6 signaling. Persistent phosphorylation of STAT1/3 is associated with high-level inflammation in cells, whereas inhibitors of the JAK/STAT pathway inhibit IFN-α/β signaling and exert immunomodulatory effects in excessive inflammatory conditions such as macrophage activation syndrome [16].

Furthermore, the activation of MAPKs (p38, ERK, JNK) regulates inflammatory cytokine production and contributes to apoptosis, necrosis, and NET formation, thereby enhancing tissue injury. The NLRP3 inflammasome promotes caspase-1-mediated maturation of IL-1β and IL-18 and induces pyroptosis, further amplifying inflammation [17, 18]. For instance, luteolin and *Scutellaria baicalensis* Georgi and *Coptis chinensis* Franch ameliorate cytokine release syndrome by mediating the NLRP3/gasdermin D (GSDMD) pyroptosis pathway and its upstream CD39 purinergic signaling [17]. LPC, however, increases NLRP3 acetylation via the GITR-MARCH7-SIRT2 axis and promotes NLRP3 overactivation and macrophage pyroptosis, thereby worsening systemic inflammatory injury [18]. ACSS2 controls the activation of NLRP3 in renal tubular epithelial cells via the KLF5/NF-κB pathway, indicating that metabolic reprogramming is closely integrated with the inflammatory response [19].

In addition to these main pathways, cellular iron metabolism and ferritin also enhance inflammation. Studies have revealed that disruptions in iron homeostasis impair the ability of myeloid immune cells to regulate NF-κB and inflammasome activities, thus posing serious pathophysiological challenges for septic patients with iron overload [20]. Epidermal growth factor receptor (EGFR) has been confirmed as an important regulator of TNFR1-mediated inflammation and RIP3-dependent necroptosis, providing theoretical support for the potential immunological mechanisms of anti-EGFR therapy in sepsis-associated ALI [21].

Collectively, these interconnected signaling pathways form self-amplifying networks that drive excessive cytokine release and immune imbalance in sepsis. To provide a systematic overview of these mechanisms, this review summarizes key pro-inflammatory cytokines, their associated signaling pathways, and regulatory features involved in the cytokine storm in **Table 1**.

2.3 Cellular communication and inflammatory cascades

The septic cytokine storm is characterized by cell-to-cell communication, which is the driving force for systemic cascading inflammation. Communication between immune cells and endothelial cells is also key to this process. They form an intricate signaling network, connected by numerous means such as direct cellular contact, excretion of soluble factors, and extracellular vesicles (EVs), thus coordinating the initiation, amplification, and resolution of inflammation. Experiments have shown that direct interaction between bone marrow-derived mesenchymal cells and macrophages greatly enhances the production of IL-6, IL-10, and nitric oxide (NO). The generation of TNF-α is also suppressed by prostaglandin E_2. As a result, bone marrow-derived mesenchymal cells may alleviate systemic inflammation and modulate tissue inflammation, thereby maintaining immune homeostasis [46]. EVs carry MFG-E8, which facilitates the complete phagocytosis of apoptotic cells and therefore decreases systemic inflammation, as well as serving a protective function in sepsis [47]. In addition, bone

Table 1. Key inflammatory mediators and signaling pathways associated with cytokine storm

Inflammatory mediator	Major signaling pathway	Downstream targets	Function/role	References
TNF-α, IFN-γ	JAK/STAT1/IRF1 axis	Caspase-8	Induces PANoptosis-mediated inflammatory cell death	[8]
IL-6	Innate immune inflammatory signaling	Acute-phase reactants	Triggers systemic fatal inflammatory response	[22]
TNF-α, IL-6	Heparanase-dependent inflammatory signaling	Endothelial glycocalyx and adhesion molecules	Promotes inflammatory responses and organ injury	[23]
Ferritin	MSR/PAD4/ROS-dependent pathway	NETs	Induces systemic inflammation and lung injury	[3]
ACOD1 (IRG1)	CDK2→MAPK8→JUN axis	TNF signaling and pro-inflammatory cytokines	Activates cytokine storm and promotes inflammatory responses	[24]
TNF-α, IL-6	HIF-1α-dependent glycolysis	Macrophage metabolism and NF-κBp65 activity	Inhibits pro-inflammatory responses and cytokine storm	[25]
Pro-inflammatory M1 macrophage cytokines	NF-κB/ERK1/2 signaling pathway	M1 macrophage activity	Inhibits cytokine storm and ALI	[26]
TNF-α, IL-1, IL-6	LPS-induced inflammatory pathway	Serum inflammation levels	Regulates pro-inflammatory mediator expression	[27]
TNF-α, IL-6	Inflammation and oxidative stress pathways	Serum inflammatory cytokines, oxidative stress	Inhibits inflammatory cytokines and alleviates oxidative stress	[28]
Pro-inflammatory cytokines	P2Y2 receptor-mediated pathway	JNK, MMP-9, iNOS, NLRP3	Alleviates liver damage, suppresses inflammation, and improves survival	[29]
IL-1β/TNF-α	NF-κB pathway	GSDMD	Exacerbates alveolar epithelial injury	[30]
Various pro-inflammatory cytokines	IDO1-AHR-CYP1A1 axis	STAT3, NF-κB/STAT1, JNK/p38	Promotes cytokine storm and cell apoptosis	[12]
IL-1β, IL-18, IL-10	Caspase-11/GSDMD	GSDMD	NAD^+ blocks GSDMD-mediated pyroptosis and promotes immune homeostasis	[31]
TNF-α, IL-1β	PD-1 checkpoint	M1 marker (iNOS)	SMEP suppresses pro-inflammatory responses	[32]
TNF-α/IL-6	HIF-1α/LDHA	ICAM-1/VCAM-1/VEGF-A	Sepsis-induced endothelial injury	[33]
IL-1β, IL-18	NLRP3 inflammasome pathway	NETs	Promotes immunothrombosis and multi-organ injury	[34]
NLRP3	P2X7-NLRP3	Caspase-1	Mediates pyroptosis and inflammatory responses	[35]
cfDNA	Activation of TLRs/NF-κB pathway	NF-κB	Activates inflammatory responses	[36]
STAT3	IL-6/STAT3	FUNDC1	Regulates MAMs formation and mediates myocardial dysfunction	[37]
TNF-α, IL-1β	FAK-Pyk2, p38 MAPK pathway	NLRP3 inflammasome	Pro-inflammatory effect	[38]
IL-6, IL-1β, TNF-α	NLRP3 inflammasome	ROS/mtROS	Mitigation of cytokine storm	[39]
IL-6, IL-1β	ERK/JNK/NF-κB pathway	PGE_2	Induces PGE_2 production and participates in inflammatory responses	[40]
Tumor necrosis factor	TLR4	Caspase 3/7	Induces apoptosis	[41]
COX-2	NF-κB	PGE_2	Produces PGE_2 and mediates inflammatory responses	[42]
TNF-α	NF-κB/Akt pathway	$CD38^+$ macrophages	Regulates the cytokine storm in sepsis	[43]
IL-1β, IL-18	NF-κB/NLRP3 inflammasome	Caspase-1	Alleviates hepatic injury in septic mice	[44]
IL-1β	NLRP3 inflammasome	KLF2	Targets therapy for neonatal sepsis	[45]

Note: TNF-α, tumor necrosis factor-alpha; IFN-γ, interferon-gamma; JAK/STAT1/IRF1, Janus kinase/signal transducer and activator of transcription 1/interferon regulatory factor 1; IL-6, interleukin-6; MSR, macrophage scavenger receptor; PAD4, peptidyl arginine deiminase 4; ROS, reactive oxygen species; NETs, neutrophil extracellular traps; ACOD1, aconitate decarboxylase 1; IRG1, immunoresponsive gene 1; CDK2, cyclin-dependent kinase 2; MAPK8, mitogen-activated protein kinase 8; JUN, Jun proto-oncogene; HIF-1α, hypoxia-inducible factor 1-alpha;

NF-κBp65, nuclear factor kappa-B subunit p65; ERK1/2, extracellular signal-regulated kinase 1/2; ALI, acute lung injury; LPS, lipopolysaccharide; P2Y2, P2Y purinoceptor 2; JNK, c-Jun N-terminal kinase; MMP-9, matrix metalloproteinase-9; iNOS, inducible nitric oxide synthase; NLRP3, NLR family pyrin domain containing 3; GSDMD, gasdermin D; IDO1, indoleamine 2,3-dioxygenase 1; AHR, aryl hydrocarbon receptor; CYP1A1, cytochrome P450 family 1 subfamily A member 1; STAT3, signal transducer and activator of transcription 3; IL-18, interleukin-18; IL-10, interleukin-10; NAD^+, nicotinamide adenine dinucleotide; PD-1, programmed cell death protein 1; LDHA, lactate dehydrogenase A; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; VEGF-A, vascular endothelial growth factor A; P2X7, P2X purinoceptor 7; cfDNA, cell-free deoxyribonucleic acid; TLRs, Toll-like receptors; FUNDC1, FUN14 domain containing 1; MAMs, mitochondria-associated endoplasmic reticulum membranes; FAK, focal adhesion kinase; Pyk2, proline-rich tyrosine kinase 2; p38 MAPK, p38 mitogen-activated protein kinase; mtROS, mitochondrial reactive oxygen species; PGE_2, prostaglandin E_2; TLR4, Toll-like receptor 4; COX-2, cyclooxygenase-2; Akt, protein kinase B; CD38, cluster of differentiation 38; KLF2, Krüppel-like factor 2; SMEP, sepsis-modified extracellular peptides.

marrow-derived mesenchymal stem cell-derived exosomes induce M2 macrophage polarization by targeting the miR-20a-5p/CXCL12 axis, thereby effectively inhibiting the septic cascade [48].

By recruiting immune cells and regulating inflammation, Meteorin-like protein can direct the migration of macrophages, which in turn dramatically increases the body's resistance to sepsis, even as it balances new controls over Treg/Th17 immunity [49]. However, via the Snail/CXCL2 axis, PAK1 can enhance the inflammatory cascade following sepsis [50]. It is worth noting that in both infectious and noninfectious systemic inflammation, IL-6 can promote TNF-α production through the NF-κB pathway rather than classical STAT3 signaling, thus making inflammatory responses more severe [51].

In sepsis, there exists a highly complex and tightly coupled intracellular signaling network. Through multiple pathways within these networks, the inflammatory cascade can spread rapidly. The mechanisms by which innate immune activation and inflammatory cell death contribute to sepsis are dissected in this review by summarizing the classical and non-classical activation processes of the inflammasome signaling pathway in **Figure 1**. Via the TLR-NF-κB pathway, pathogen-associated molecular patterns induce the expression of pro-IL-1β and NLRP3. LPS can activate non-classical pathways mediated by caspase-11; this in turn leads to formation of the NLRP3-apoptosis-associated speck-like protein containing a CARD (ASC)-caspase-1 complex, in which GSDMD is cleaved and N-terminal pores are formed. This can induce pyroptosis and promote the maturation and release of IL-1β, thereby amplifying dysregulated inflammation and aggravating organ dysfunction during sepsis. As the understanding of these communication and signaling networks becomes more profound, the etiology of the cytokine storm is revealed, providing both a theoretical basis and a strategy for precise anti-inflammatory intervention by regulating major pathways or EV release.

3 PATHOPHYSIOLOGICAL MECHANISMS OF SEPSIS

3.1 Microcirculatory dysfunction and organ failure

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Microcirculatory failure represents one of the key pathophysiological mechanisms underlying organ dysfunction in sepsis. This non-physiological state not only fails to provide acceptable tissue perfusion but also exacerbates the course of multiorgan failure [52, 53]. In sepsis, elevated PCSK9 levels can activate the TLR4/MyD88/NF-κB and NLRP3 pathways, thereby promoting dysregulated systemic inflammation and endothelial injury that contribute to organ dysfunction [54]. Concurrently, endothelial cell activation, upregulation of adhesion molecules, and increased vascular permeability enhance plasma extravasation and tissue hypoperfusion. Increased expression of Mac-1 on the neutrophil surface induces pulmonary microcirculatory dead space, and inhibitors of Mac-1 can partially improve ALI in sepsis, suggesting that microcirculatory perfusion abnormality is an important feature during organ dysfunction [55].

Microthrombosis is also a significant cause of microvascular dysfunction in sepsis. TNF-α, IL-1β, and HMGB1-associated proinflammatory signals promote both platelet aggregation and fibrin deposition, leading to subsequent capillary occlusion and non-uniform blood flow. Furthermore, high PAI-1 levels represent a disseminated intravascular coagulation state with suppressed fibrinolysis and are strongly related to organ dysfunction [53]. Reduced erythrocyte deformability and reduced blood flow worsen tissue hypoxia, such that microcirculatory perfusion may be impaired despite normal blood flow in the larger vessels, leading to a mismatch between perfusion and oxygenation even when large vessel blood flow is unimpaired [52]. Both clinical and experimental studies have demonstrated that septic shock is associated with peripheral vascular hyporesponsiveness, although some capillary beds within the post-capillary circulation retain residual responsiveness [56]. These findings imply that vasomotor regulatory function is an important factor in sustaining microcirculatory integrity.

Some interventions targeting microcirculatory failure have beneficial effects. For instance, Shenfu Injection enhances microcirculatory perfusion and endothelial function through suppression of PI3K/Akt-induced glycolysis [57]. Salvianolic acid B, meanwhile, mitigates microcirculatory failure and sepsis progression by suppressing platelet CD226 molecule function [58]. Multiple factors, including endothelial damage, an overwhelming inflammatory response, microthrombosis,

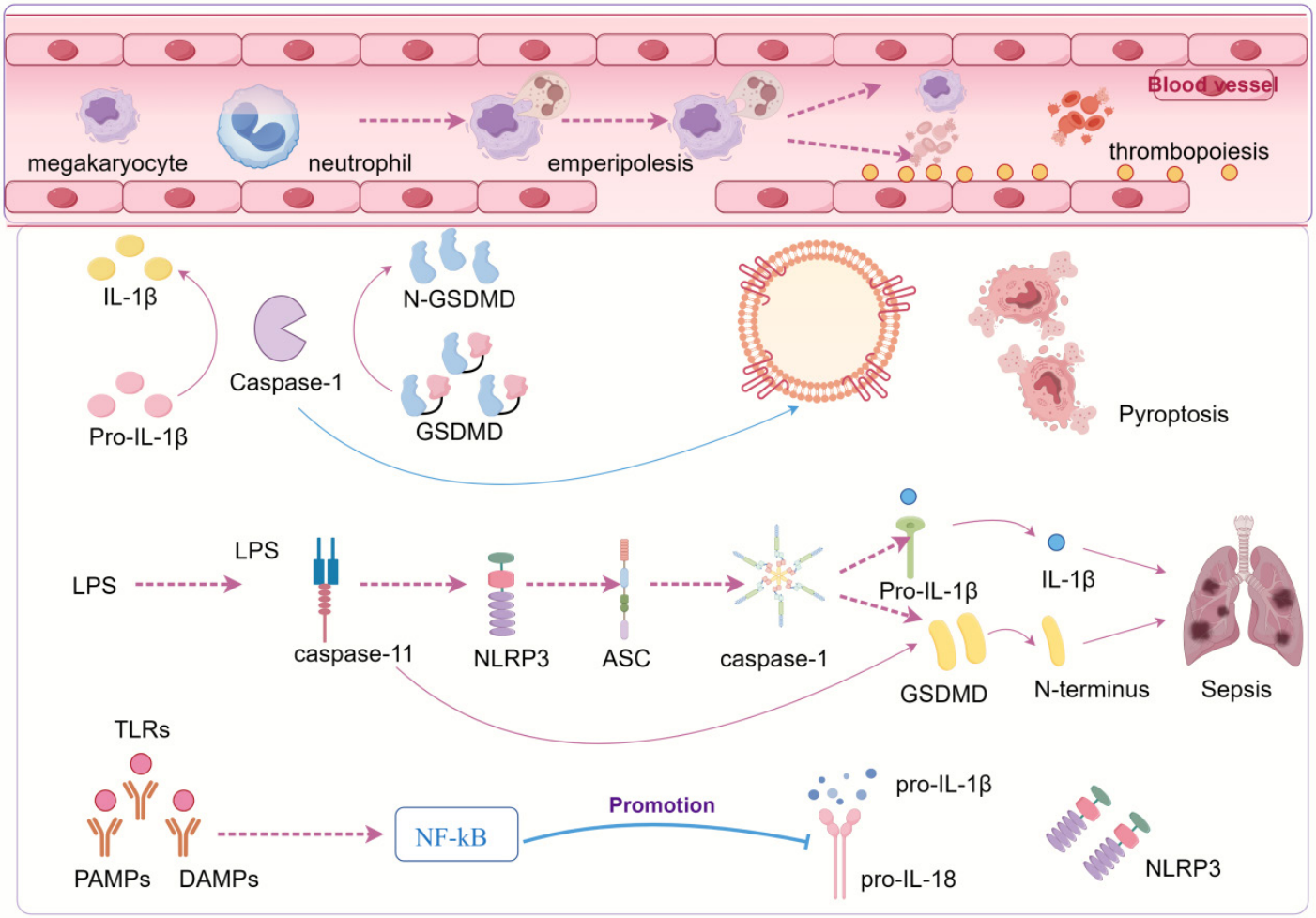

Figure 1. Mechanistic diagram of inflammasome activation and pyroptosis in sepsis and thrombopoiesis. This diagram illustrates how inflammasome activation contributes to excessive inflammatory responses and subsequent organ dysfunction during sepsis, as well as to platelet formation via GSDMD-driven pyroptosis. TLRs recognize PAMPs and DAMPs and then activate NF-κB signaling, prompting the expression of pro-inflammatory cytokines such as pro-IL-1β and pro-IL-18, as well as NLRP3. Activation of caspase-11 by LPS contributes to NLRP3 inflammasome assembly, and caspase-1 is also activated at the plasma membrane via the adaptor protein ASC. N-GSDMD can form membrane pores, thereby enabling pyroptosis as well as the release of IL-1β. Thus, in sepsis model mice, this process accelerates both systemic inflammation and disease progression. The inset graph illustrates emperipolesis occuring between neutrophils and megakaryocytes. It suggests that this specific cellular response leads to both enhanced platelet formation and amplification of inflammation in the local vascular environment.

and imbalanced oxygen delivery, play a role in the pathogenesis of septic microcirculatory dysfunction. These mechanisms interact to generate a complex network, resulting in multiorgan failure. This explains the clinical approach toward multitarget interventions (microcirculation protection, anti-inflammatory treatment, and antithrombosis therapy).

3.2 Pathogen recognition and host response

Sepsis is a severe syndrome caused by microbial infection and characterized by excessive host inflammatory responses and organ injury [59]. In this process, pathogen-associated molecular patterns and damage-associated molecular patterns are recognized by pattern recognition receptors expressed on epithelial and endothelial cells of barrier tissues, as well as on circulating and resident innate immune cells, thereby initiating early innate immune responses. This represents a generalized mechanism of early host–pathogen interaction in sepsis rather than a process restricted to a specific anatomical site or experimental model, thereby triggering the initial immune defense [60].

Neutrophils assemble inflammasome complexes in distinct subcellular compartments and, in sepsis-relevant models, predominantly release mature IL-1β and IL-18. In these settings, extracellular IL-1α and IL-33 are often minimal or undetectable, indicating a context-dependent and selective inflammasome-associated cytokine output rather than a universal paradigm. This suggests that the pro-inflammatory function of the inflammasome during sepsis is highly selective [60].

Table 2. Pathophysiological mechanisms and clinical manifestations associated with sepsis

Inflammatory cytokines	Key signaling pathways	Downstream targets	Functions/effects	References
NLRP3 inflammasome	Calcium influx-mediated pathway	Caspase-1	Exacerbates inflammatory responses in sepsis	[72]
TNF-α	NF-κB	NLRP3	Induces macrophage pyroptosis associated with sepsis	[73]
HMGB1	RAGE–LPS internalization pathway	Caspase-11	Mediates pyroptosis and sepsis-induced lethality	[74]
IL-1β	NLRP3 inflammasome pathway	NF-κB	Leads to sepsis-associated myocardial atrophy and contractile dysfunction	[75]
TNF-α, IL-6	CD14/Syk/PLCγ2 pathway	MyD88	Excessive inflammation contributes to the development of sepsis	[76]
IL-1β	Caspase-11-GSDMD pathway	NLRP3 inflammasome	Mediates pyroptosis and septic shock	[77]
miR-21	ADAR1/miR-21/A20 axis	NLRP3 inflammasome	Inhibits macrophage pyroptosis induced by sepsis	[78]
TNF-α	TAK1/NF-κB/MAPKs, Nrf2 pathways	TAK1, Keap1	Ameliorates sepsis	[79]
IL-6	gp130–JAK2–STAT3 pathway	SOCS3 gene expression	Mediates muscle atrophy in sepsis	[80]
IL-1β	Pyroptosis pathway	GSDMD	NSA inhibits pyroptosis to alleviate sepsis	[81]
IL-1β/IL-6/TNF-α	Notch1–NF-κB pathway	Tight junction proteins	Regulates sepsis-associated gut–brain axis inflammation	[82]
IL-6	IL-6/STAT3 signaling pathway	STAT3	Suppresses inflammation and apoptosis in sepsis	[83]
GDF15	AMPK/NF-κB/MAPK pathways	eIF2α/ATF4 transcription axis	Inhibits sepsis-associated inflammation and glycolysis	[84]
IL-1β	NLRP3 inflammasome pathway	Tissue factor	Promotes sepsis-associated coagulation and thrombosis	[85]
TNF-α/IL-6	TLR4 signaling pathway	LC3-II/p62	Promotes anti-inflammatory responses and activates autophagy during sepsis	[86]
IL-1β	ADRA2B-cAMP-PKA pathway	GSDMD cleavage	Inhibits sepsis-associated pyroptosis	[87]
Citrullinated histone H3	TLR2-Ca^{2+}-PAD2 axis	PAD2 auto-citrullination and nuclear translocation	Promotes sepsis-associated NETs pyroptosis	[88]
IL-1β	NLRP3 inflammasome pathway	Mitochondrial ROS and autophagy	Inhibits sepsis-associated inflammasome activation	[89]
TNF-α/IL-6/IL-1β	STAT3/NF-κB/NLRP3 pathways	GPR18	Alleviates ALI induced by sepsis	[90]
IL-1β/IL-6/TNF-α/MCP-1	miR-122-5p–HO-1/MASP1 pathway	MASP1/HO-1	Regulates sepsis-associated coagulation and inflammatory responses	[91]
TNF-α/IL-6/IL-1β	TLR4/MAPK/NF-κB pathway	TLR4–MD2 complex	Inhibits the production of sepsis-associated inflammatory cytokines	[92]
TNF-α, IL-6	NF-κB pathway	VCAM-1/ICAM-1	Attenuates sepsis-induced ALI	[93]
IL-1β	NLRP3 inflammasome pathway	NLRP3, caspase-1	Inhibits sepsis-associated pyroptosis	[94]
TNF-α/IL-1β	NF-κB pathway	TRPM7	Reverses LPS-induced septic cardiomyocyte injury	[95]
GPIbα cytoplasmic tail–mediated regulation of inflammatory cytokines	PKC-dependent pathway	GPIbα cytoplasmic tail	Exacerbates sepsis-associated platelet activation and inflammation	[96]
TNF-α, IL-6, IL-1β	Ubiquitination–lactylation pathway	CDT2–KAT2A axis	Ameliorates myocardial injury in septic cardiomyopathy	[97]
IL-1β, IL-6, TNF-α	NF-κB inflammatory pathway	NFKBIA mRNA	Alleviates neuroinflammation in sepsis-associated encephalopathy	[98]

Note: NLRP3, NLR family pyrin domain containing 3; TNF-α, tumor necrosis factor-alpha; NF-κB, nuclear factor kappa-B; HMGB1, high mobility group box 1; RAGE, receptor for advanced glycation end products; LPS, lipopolysaccharide; IL-1β, interleukin-1 beta; IL-6, interleukin-6; CD14, cluster of differentiation 14; Syk, spleen tyrosine kinase; PLCγ2, phospholipase C gamma 2; MyD88, myeloid differentiation primary response 88; GSDMD, gasdermin D; miR-21, microRNA-21; ADAR1, adenosine deaminase acting on RNA 1; A20, tumor necrosis factor alpha-induced protein 3 (TNFAIP3); TAK1, transforming growth factor-beta-activated kinase 1; MAPKs, mitogen-activated protein kinases; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; gp130, glycoprotein 130; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; SOCS3, suppressor of cytokine signaling 3; NSA, necrosulfonamide; Notch1, neurogenic locus notch homolog protein 1; GDF15, growth differentiation factor 15; AMPK, AMP-activated protein kinase; eIF2α, eukaryotic initiation factor 2 alpha; ATF4, activating transcription factor 4; TLR4, Toll-like receptor 4; LC3-II, microtubule-associated protein 1 light chain 3-II; p62, sequestosome-1; ADRA2B, adrenoceptor alpha 2B; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; PAD2, peptidyl arginine deiminase 2; ROS, reactive oxygen species; GPR18, G protein-coupled receptor 18; ALI, acute lung injury; MCP-1, monocyte chemoattractant protein-1; HO-1, heme oxygenase-1; MASP1, mannan-binding lectin serine protease 1; MD2, myeloid differentiation factor 2; VCAM-1, vascular cell adhesion molecule 1; ICAM-1, intercellular adhesion molecule 1; TRPM7, transient receptor potential melastatin 7; GPIbα, glycoprotein Ib alpha chain; PKC, protein kinase C; CDT2, full name to be confirmed, a RING-type E3 ubiquitin ligase; KAT2A, lysine acetyltransferase 2A; NFKBIA, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha.

In monocytes, TLR agonists induce an overall similar pattern of glycoprotein expression changes, but the profile changes under *Staphylococcus aureus* stimulation is partially distinct. Eleven glycoproteins (CD44, CD274, LILRB1, ICAM1, DSC2, PTGS2, LAMP3, CR1, FGL2, HP, and SLC1A3) are consistently dysregulated in the tolerant cell state [61].

C-ter100 can activate NF-κB through TLR4 and promote TNF-α and NO generation, as well as provoke NLRP3 inflammasome assembly (NLRP3, ASC, caspase-1) and IL-1β secretion [62]. Loss of nucleic acid recognition is likely to contribute to the lack of early detection of *S. pyogenes*, diminishing local infection control and ultimately initiating systemic inflammation at later stages [63]. Expression and regulation of monocyte TLR-2 may be abnormal in septic patients, whereas those for TLR-4 are relatively low [64].

Peritonitis can increase expression of peritoneal exudate cells genes involved in sepsis but does not augment this response after LPS pretreatment [65]. FLAP and 5-LO-dependent eicosanoids are also involved in bacterial endotoxin-induced inflammation through TLR-dependent mechanisms [66]. Genetic background, gut microbiota composition, and metabolic status modulate the magnitude and kinetics of the host immune response. Together, these components of the ambivalent inflammatory response in sepsis dictate whether pathogen elimination through inflammation, or instead, characteristic hyperinflammation will prevail.

3.3 Metabolic reprogramming and cell death

Metabolic reprogramming and pyroptosis during sepsis progression are mutually intertwined, propagating the inflammatory response and ultimately resulting in multiorgan failure. It has been reported that these interventions, including scavenging of lipid peroxidation by the antioxidant vitamin E, chemical inhibition of PLCG1, and gene deletion for Caspase-11/GSDMD, could significantly modulate ferroptosis and other metabolism-dependent cell death pathways and ameliorate tissue damage induced by polymicrobial sepsis [67].

EGFR mediates the membrane translocation of Glut1 via the downstream TBK1/Exo84/RalA protein pathway, which results in Warburg effect. This reinforces the activation and apoptosis of $CD4^+$ T lymphocytes, further resulting in damage to immune function and contributing to accelerated immunological exhaustion. Furthermore, IL-1R2 physically interacts with enolase 1, which can suppress glycolysis-mediated pyroptosis and inflammation, thus indicating a therapeutic target within this pathway. Dexmedetomidine can also help maintain metabolic balance by upregulating Nrf2, inhibiting mitochondrial fission, and downregulating ferroptosis and vascular leakage [68]. Meanwhile, aerobic glycolysis suppression can activate autophagy via the lactate/SIRT3/AMPK signaling pathway, thereby providing protection in sepsis-associated acute kidney injury (AKI) [69].

Mechanistically, ferroptosis and lipophagy contribute significantly to septic AKI, which has added new insight into the pathogenetic mechanisms and therapeutic targets of AKI [70]. Moreover, knockout or knockdown of MAPL also attenuates septic myocardial injury and inflammation by inhibiting Drp1 SUMOylation and ameliorating mitochondrial dysfunction. These findings suggest that metabolic reprogramming and multimodal cell death are tightly interconnected in sepsis and together contribute to a dysregulated host response to infection, characterized by excessive inflammation followed by immune suppression, which ultimately results in life-threatening organ dysfunctions [71].

Energy metabolism pathways can be regulated, selected forms of cell death can be inhibited, and autophagy can be stimulated, resulting in attenuation of the organ injury response and systemic inflammation. To systematically reveal the pathological processes and clinical manifestations critically associated with sepsis development, priority mechanisms are summarized in **Table 2**. The pathophysiology of sepsis is complex and multifaceted, comprising interactions among immune dysfunction, microcirculatory derangement, metabolic disarray, and cell death networks. These mechanisms collectively contribute to the progression from localized infection to dysregulated sys-

temic host response and subsequent organ dysfunction: microcirculatory dysfunction induces tissue hypoxia; abnormal recognition and/or excessive response to pathogens will excessively activate the immune system; and metabolic disorders activated by these former processes, along with programmed cell death itself, further enhance inflammation-induced injury. This mechanistic framework informs the pathogenesis of sepsis and identifies core nodes with their intrinsic relationships at different levels, from molecule to system, thus offering theoretical support for early identification and multi-target combination interventions.

4 REGULATION AND DYSREGULATION OF IMMUNE RESPONSES

4.1 Immunosuppressive phase and immune evasion

Studies have demonstrated that the immunosuppressive phase of sepsis involves sophisticated immune regulation and evasion, which are mediated through broad interplays among cellular functions, metabolism, and signaling. Neutrophils with high expression of CD200 receptor may also induce systemic immunosuppression by promoting Treg cells [99]. Indeed, recent investigations also indicate that metabolic reprogramming acts as a pivotal mediator of crosstalk between immune cell subsets in sepsis. Inflammatory stress and hypoxia direct immune cells into a state of increased glycolysis and modified lipid metabolism, resulting in remodeling of immune differentiation and functional polarization. Metabolic rewiring, for instance, skews T-cell subsets toward regulatory phenotypes, and lactate accumulation inhibits effector T-cell responses. Macrophage polarization is tightly associated with metabolic state. These results suggest that metabolic changes actively drive immune subset dysregulation during sepsis and are not simply a reflection of immune activation [100]. This indicates that intracellular metabolic regulation could be a novel therapeutic approach for sepsis-induced immunosuppression [101]. $CXCR2^+$ neutrophil subtypes also participate in immune suppression, which may warrant their consideration as therapeutic targets [102].

TCF7 and LEF-1 overexpression can significantly upregulate the proliferation capability and effector function of $CD4^+$ T cells, inhibit sepsis-induced apoptosis, and downregulate the expression of PD-1/LAG-3, resulting in a stronger immune response in patients with sepsis [103]. Metabolic dysfunctions have an intrinsic role in immunosuppression: lactate impairs T cell activation by downregulating CD40LG and SOCS3 expression, consequently restraining the JAK-STAT signaling pathway [104]. Low-density neutrophils suppress T cells through PD-L1 and contribute to susceptibility to secondary infections [105]. Neutrophil immune function can be compromised by glycolysis blockage, which downregulates lactate dehydrogenase A via the PI3K/Akt-HIF-1α signaling pathway [106]. The Spns2/S1P signaling pathway is important for regulating immune homeostasis, inhibiting excessive early inflammation, and relieving delayed immunosuppression, which may have a critical role in immune remodeling [107].

These investigations systematically demonstrate the hallmarks of regulatory networks in the immunosuppressive process of sepsis and underscore that the generation of Treg cells, subset properties of neutrophils, and dysregulated cellular metabolism are crucial hubs for immune evasion. They support rational drug discovery targeting metabolic reprogramming, immune checkpoint regulation, and signaling pathways.

4.2 Negative feedback mechanisms and host homeostasis

Targeted deletion of IL-10 in $CD169^+$ macrophages results in dramatically increased mortality during septic challenge, and administration of recombinant IL-10 is protective in a model of LPS-induced lethality, thereby highlighting the importance of anti-inflammatory mediators during early negative feedback regulation of inflammation [108, 109]. Adenosine deaminase acting on RNA 1 (ADAR1) inhibits sepsis-related ALI by suppressing the activation of pyroptosis in pulmonary macrophages via the miR-21/A20/NLRP3 axis, demonstrating that the host provides a possible negative feedback-based control mechanism to prevent inflammation propagation and tissue damage at the molecular level [78]. In patients with sepsis, T cell immunoreceptor with Ig and ITIM domains $(TIGIT)^+$ T cells display PD-1 upregulation, CD226 downregulation, and impaired cytokine secretion, remarkably, in vitro blocking of TIGIT restores T cell activity. These results imply that the inhibitory receptor modulates T cell activity through negative signaling to balance the immune response and avoid excessive inflammation [110].

The IL-10/DEL-1 axis not only favors emergency granulopoiesis over neutropenia but also promotes early host survival by balancing the abundance and function of immune cells, thus emphasizing the role of immune negative feedback in inducing overall immune homeostasis [108, 109, 111]. In addition, the finding that the absence of IL-10 in B cells leads to aberrant cGMP-PKG signaling, and that exogenous IL-10 supplementation alleviates LPS-induced ALI, suggests that negative feedback loops maintain both local and systemic immune homeostasis through dense network interactions with cytokines and immune cells [111]. In CLP-induced sepsis survivor mice, splenic $CD11b^+$ $Ly6C^{high}$ myeloid cells are significantly expanded at 4 weeks post-injury, and are predominantly composed of monocytic myeloid-derived suppressor cells with evident metabolic reprogramming. Overall, this population exhibits M-MDSC–like metabolic features, suggesting that immunosuppressive myeloid cells participate in post-inflammatory immune regulation after sepsis in a dynamic and adaptive manner [112].

IL-4 induces LAMP2 expression by activating STAT3 in lysosomal homeostasis and autophagic flux, and this metabolic and cellular homeostatic regulation is also involved in negative feedback control [113]. Furthermore, artemisinin-based therapy rescues both inflammatory and immunosuppressive states in sepsis immune cells, therefore globally restoring the homeostasis of the host's immunological defense function, suggesting that these negative feedback mechanisms play an integrative regulatory role in controlling host defense.

4.3 Role of immunoregulatory cells

During the development of sepsis and the cytokine storm, immunoregulatory cells are critically involved in the regulation of host immune homeostasis and the downregulation of excessive inflammation. They inhibit hyperactivation of effector T cells, dendritic cells, and other immune-activated cells through the growth factors IL-10 and TGF-β, as well as through contact-mediated inhibitory mechanisms, thus locally restricting inflammation to control tissue damage. Production of reactive oxygen species and NO by MDSCs is the most common mechanism to inhibit T cell proliferation, as well as to control amino acid metabolism pathways and the inflammatory activity of macrophages and neutrophils. At the height of inflammation, the explosive accumulation of MDSCs acts to protect tissues from injury, while their protracted survival can contribute to immunosuppression.

Local immune self-regulation, however, is still modulated by tissue-resident regulatory macrophages and dendritic cell subtypes that not only produce anti-inflammatory/proresolving mediators and phagocytose apoptotic cells but also regulate the expression of co-stimulatory molecules to dampen hyperresponsiveness, thereby essentially inhibiting overt inflammatory responses. At the molecular level, Nrf2 plays a role in protecting against sepsis-induced lung injury by modulating autophagy and NF-κB/PPARγ-dependent macrophage polarization [114]. GPR174 affects early immune regulation in sepsis by altering macrophage phenotype and the production of both pro- and anti-inflammatory cytokines [10]. In addition, the 'mature DCs enriched in immunoregulatory molecules' program is activated within 24 hours after sepsis onset via the TNFRSF-NF-κB and IFNGR2-JAK-STAT3 pathways, highlighting the critical role of dendritic cells in early immune modulation [115].

PAD2/PAD4 deletion restrains NLRP3 activation and accelerates the resolution of inflammation by skewing the $Ym1^+$ M2 macrophage phenotype toward a resolving phenotype in the lungs. Thus, the PADIs/NLRP3/Ym1 axis may be a novel therapeutic target for sepsis-associated ALI [116]. Repeated sepsis worsens $CD4^+$ T cell exhaustion and the antiviral immune response, leading to poor outcomes; administration of anti-TIGIT monoclonal antibodies can reverse T cell apoptosis caused by sepsis and significantly improve survival [117, 118]. Overall, dynamic regulation of Tregs, MDSCs, regulatory macrophages, and dendritic cells, combined with the factors involved in these key signaling pathways, constitutes a complicated immunoregulatory network in sepsis and provides an excellent theoretical basis for precision intervention and targeted treatment.

5 INNOVATIVE INTERVENTIONAL STRATEGIES

5.1 Precision medicine and personalized therapy

BAM15 promotes mitochondrial DNA-dependent responses and may serve as a potential companion biomarker for the initial diagnosis and efficacy monitoring of septic patients during therapy [119]. The immune response in sepsis is highly variable, and this heterogeneity has a profound impact on disease outcome and its treatment. Integrated analysis of patients' immune phenotypes, metabolic status, microbiome information, and genetic content leads to accurate stratification of the intensity and type of inflammatory responses and provides a solid scientific foundation for personalized interventions [120]. A typical application scenario may involve the patient population with a low resistance program molecular fingerprint compared with systemic inflammation levels, for which greater diversity of immune states is relevant for developing more sophisticated stratification strategies and adjustment of therapeutic schedules.

Certain combinations of IFN-γ and IL-1β can efficiently differentiate cytokine release syndrome from sepsis, thus significantly enhancing the accuracy of individualized therapeutic interventions [121]. Neutrophil-derived C1q has been proposed as a consistent prognostic biomarker for sepsis-associated death and could be a therapeutic target [122]. Furthermore, the transfer of apoptotic cells to patients with mild-to-moderate sepsis has been found to be safe and feasible, capable of directing immune responses and contributing to early termination of the cytokine storm [123]. As an essential autophagy-regulatory molecule, RAS protein activator-like 3 not only plays a role in the treatment of sepsis but also provides a new therapeutic target for other inflammatory conditions [124].

Using precise risk factors, such as the Acute Physiology and Chronic Health Evaluation III score, bicarbonate levels, anion gap, and invasive/noninvasive systolic blood pressure in combination, more personalized therapies can be tailored to improve survival time and prognostic outcomes in patients with sepsis-induced acute respiratory distress syndrome [125]. Furthermore, the heterogeneity of sepsis subtypes and differences in mortality among populations have been observed; such a tri-variable model can effectively identify patients with the δ sepsis subtype and thus form a reliable basis for dynamic monitoring and stratified intervention [126]. Integration of high-throughput multi-omics techniques, single-cell transcriptomic profiling, and AI algorithms allows real-time monitoring

of immune cell subsets and inflammatory networks. This holistic approach can offer an evidence-based strategy for appropriate drug choice, medication dosage, and timing of intervention in the cytokine storm to maximize its control, reconstitute immune balance, and ultimately improve patient outcomes.

5.2 Application of biomarkers in clinical decision-making

In independently predicting mortality among septic patients, lactate performs better than the quick sequential organ failure assessment (SOFA) score and equally well as the full SOFA score [127]. To improve translational clarity, the discussed biomarkers are interpreted within a phenotype-oriented framework. Sepsis-associated cytokine storms may manifest as hyperinflammatory, immunosuppressive, endothelial/organ dysfunction-dominant, or hypoperfusion/metabolic phenotypes. Rather than being viewed as isolated indicators, biomarkers should therefore be contextualized within these immune states to guide risk stratification and therapeutic prioritization [128]. EV-derived miRNAs may help differentiate sepsis from non-septic shock, and a three-miRNA composite can substantially enhance diagnostic potential, serving as an ideal decision-making tool for early intervention in this critical group of postoperative subjects [129]. The combination of serum CD64 and pro-adrenomedullin with the SOFA score has good discriminatory capability in patients with septic shock. Of these markers, CD64 is easier to detect and more convenient; it can partly replace complicated scores [130]. The Systemic Immune-Inflammation Index and procalcitonin have both demonstrated potential value in the prognostic assessment of sepsis, and their combined application may further improve the predictive accuracy for adverse outcomes in septic shock. However, current findings remain heterogeneous, and their clinical utility still requires further validation [131]. Early increased PTX3 levels in severe sepsis and septic shock are associated with the development of new organ dysfunction, while a smaller decrease in circulating PTX3 levels is associated with an unfavorable prognosis. Interestingly, in patients with septic shock undergoing albumin resuscitation, PTX3 levels are lower than in those receiving crystalloids [132]. BMP9 has been identified as a stratification biomarker with independent prognostic value, serving as a potential host-targeting strategy for sepsis treatment [133]. Evidence indicates that time-restricted feeding plays a hepatoprotective role in sepsis-induced hepatic injury, and 3-HB might represent a novel pharmacological target, and even a serum marker, for the treatment of severe liver injury of unknown cause, which could provide new ideas for the clinical treatment and risk assessment of hepatic injury [134]. Serum CXCL5 levels have also been suggested as a useful biomarker for enhancing sepsis diagnosis and outcome prediction, and can therefore be used in multivariate predictive models for better risk stratification and to guide treatment initiation [135].

However, no single biomarker can fully capture the complexity of the inflammatory network in sepsis, further supporting the need for phenotype-oriented multimarker integration. Multimarker composite features—such as lactate, cytokine profiles, immune cell functions, and metabolism—can offer a more accurate determination of patients' inflammatory status and immune competence for early intervention and personalized therapy. Continuous monitoring of important inflammatory mediators and immune parameters allows closer guidance of therapy with anti-infective and immunomodulatory drugs in real time, optimizing therapy duration and avoiding over-immunosuppression or overactivation. In an era of progressive development in single-cell analysis, metabolomics, and AI-driven predictive models, the clinical value of these biomarkers is anticipated to achieve a higher level of precision and personalization, providing firm support for accurate patient stratification and identification, tailored interventions, and improved outcomes in sepsis, and ultimately reducing sepsis-associated mortality.

5.3 Novel immunomodulators and anti-inflammatory agents

At the same time, the translational relevance of immunomodulatory spectra in sepsis becomes more substantive when treatment is specifically targeted to biologically delineated immune endotypes. Interventions such as adjunctive corticosteroids, rather than being applied uniformly, may be more properly considered within gene-expression-informed inflammatory states, which can identify patients likely to benefit most and mitigate the potential harms of indiscriminate immune suppression [136]. Sepsis and its attendant cytokine storm represent a condition of intricate immunopathobiology, characterized by marked dysfunction and dysregulation of the host immune response, including excessive activation of inflammation in conjunction with immunosuppression and multiple organ failure. In the context of increasingly deeper integration of omics technologies and AI, the therapeutic concept of sepsis has also been transforming from traditional anti-infection or supportive care to one involving precision stratification, dynamic monitoring, and multidimensional intervention. The multi-targeted regulation modes of immune disturbance, metabolic dysfunction, and inflammatory overreactions present challenges for patient therapy. In summary, to systematically summarize recent developments and prospects in sepsis treatment, this review addresses emerging interventional strategies reported in the past decade in **Table 3**, including precision medicine, biomarker-guided management, and immunomodulatory therapy, which may provide theoretical support for a personalized medicine-oriented individualized therapeutic approach as well as combined multi-target interventions.

In addition, melittin was demonstrated to relieve sepsis-induced AKI by suppressing ferroptosis mediated by the GPX4/NRF2 signaling [159]. GDF15 protects against sepsis-induced pulmonary injury by activating AMPK, inhibiting glycolysis, and inactivating the NF-κB/MAPK signaling pathways, leading to

Table 3. Innovative intervention strategies and application prospects

Intervention strategy	Target/mechanism	Research stage	Clinical/experimental outcomes	References
TaoHe ChengQi decoction	Nrf2-mediated anti-ferroptosis pathway	Validated in animal models	Improved sepsis-induced cardiac dysfunction	[137]
NLRP3 gene knockout	NLRP3/IL-1β signaling axis	Mechanistic validation in animal models	Ameliorated sepsis-induced myocardial atrophy	[75]
EphA4-Fc decoy receptor	Blockade of Eph/Ephrin signaling	Validated in animal models	Attenuated vascular leakage and endothelial dysfunction in septic mice	[138]
Biomimetic nanoregulator	Regulation of the Nrf2/HO-1 pathway	Validated in animal models	Improved cognitive function in sepsis-associated encephalopathy	[139]
Xuebijing	NF-κB pathway	Experimental validation stage	Reduced IL-1β expression levels in patients with sepsis	[140]
UDCA	Inhibition of the STING–PANoptosis axis	Validated in animal models	Alleviated sepsis-induced pulmonary edema and inflammation	[141]
FRC-derived exosomes	CD5L–PINK1/Parkin axis	Validated in mouse models	Improved renal function and increased survival rate in sepsis	[142]
CXCR1/2 inhibition	NETosis–CXCR1/2 axis	Validated in mouse models	Reduced multiorgan injury and mortality in sepsis	[143]
miR-223 macrophage therapy	Inhibition of glycolysis and maintenance of an anti-inflammatory phenotype	Validated in mouse models	Alleviated the severity of sepsis	[144]
MALAT1–STAT3 axis inhibition	Degradation of MALAT1 and p-STAT3	Validated in mouse models	Improved survival in septic mice	[145]
Palmatine	Notch1/NF-κB pathway	Validated in mouse models	Improved neurological function in mice with sepsis-associated encephalopathy	[82]
MON targeting the AKT pathway	AKT/GSK3β/Fyn/NRF2 axis	Validated in cell and animal models	Alleviated sepsis-induced acute liver injury	[146]
Patelet NLRP6 inhibition	NLRP6–TRIM21/TAB1 axis	Validated in NLRP6 knockout mice	Reduced microvascular thrombosis in sepsis	[147]
Dapagliflozin	PI3K/Akt anti-apoptotic pathway	Validated in rat and cell models	Improved sepsis-induced cardiac dysfunction	[148]
FGR kinase inhibitor	SIRT1/PGC-1α pathway	Validated in mouse models	Improved cognitive dysfunction associated with sepsis	[149]
Rhodiola rosea extract	Inhibition of the PI3K-AKT pathway	Validated in cell and animal models	Suppressed inflammation, oxidative stress, and apoptosis in sepsis	[150]
FGF1	Inhibition of the IL-6/STAT3 pathway	Validated in cell and animal models	Alleviated coagulation dysfunction and liver injury in sepsis	[83]
ELT-mediated metabolic reprogramming	Regulation of macrophage polarization	Validated in cell and animal models	Improved sepsis-induced ALI	[151]
IL-40 gene knockout	Inhibition of S100A8/9-positive neutrophils	Validated in clinical cohorts and animal models	Reduced mortality in sepsis	[152]
Xiaochaihu decoction	Inhibition of the ZBP1–PANoptosis pathway	Validated in cell and animal models	Improved sepsis-associated cardiac function and inflammation	[153]
TIFA gene knockout	Mitochondrial damage-induced pyroptosis	Validated in cell and animal models	Alleviated sepsis-induced renal injury and inflammation	[154]
Gelsevirine	Inhibition of the STING–pyroptosis pathway	Validated in animal and cell models	Improved sepsis-associated encephalopathy	[155]
MSM immunomodulatory therapy	Lactate–H3K18la–Arg1 pathway	Validated in animal and cell models	Reduced sepsis-associated systemic inflammatory response	[156]
Activation of the VDR/FFAR2 axis	Inhibition of macrophage ferroptosis	Validated through bioinformatics analysis and cell experiments	Alleviated sepsis-associated lung injury and inflammation	[157]
Bacterial ATP release blockade	Inhibition of bacterial ATP synthase and disruption of outer membrane integrity	Validated in animal and bacterial models	Attenuated neutrophil activation during sepsis	[158]
Mollugin anti-inflammatory therapy	Inhibition of TAK1–NF-κB/MAPKs and activation of Nrf2	Validated in mouse CLP sepsis model	Alleviated pulmonary and hepatic inflammation in septic mice	[79]

Note: Nrf2, nuclear factor erythroid 2-related factor 2; NLRP3, NLR family pyrin domain containing 3; IL-1β, interleukin-1 beta; EphA4, ephrin type-A receptor 4; Fc, fragment crystallizable; HO-1, heme oxygenase-1; NF-κB, nuclear factor kappa-B; UDCA, ursodeoxycholic acid; STING, stimulator of interferon genes; PANoptosis, pyroptosis-apoptosis-necroptosis; FRC, fibroblastic reticular cell; CD5L, CD5 molecule-like; PINK1, PTEN-induced putative kinase 1; CXCR1/2, C-X-C chemokine receptor type 1/2; NETosis, neutrophil extracellular trap formation; miR-223, microRNA-223; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; STAT3, signal transducer and activator of transcription 3; p-STAT3, phosphorylated STAT3; Notch1, neurogenic locus notch homolog protein 1; AKT, protein kinase B; GSK3β, glycogen synthase kinase 3 beta; Fyn, Fyn proto-oncogene; NRF2, nuclear factor erythroid 2-related factor 2; NLRP6, NLR family pyrin domain containing 6; TRIM21, tripartite motif-containing protein 21; TAB1, TGF-beta-activated kinase 1 binding protein 1; PI3K, phosphoinositide 3-kinase; Fgr, Gardner-Rasheed feline sarcoma viral oncogene homolog; SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; FGF1, fibroblast growth factor 1; IL-6, interleukin-6; ELT, esculetin; ALI, acute lung injury; IL-40, interleukin-40; S100A8/9, S100 calcium-binding protein A8/A9; ZBP1, Z-DNA binding protein 1; TIFA, TRAF-interacting protein with forkhead-associated domain; MSM, methylsulfonylmethane; H3K18la, histone H3 lysine 18 lactylation; Arg1, arginase 1; VDR, vitamin D receptor; FFAR2, free fatty acid receptor 2; ATP, adenosine triphosphate; TAK1, transforming growth factor-beta-activated kinase 1; MAPKs, mitogen-activated protein kinases; CLP, cecal ligation and puncture.

anti-inflammatory polarization of alveolar macrophages [84]. NWG specifically inhibits Src, AKT1, and cyclooxygenase-2 (COX-2) to suppress the Src/AKT1/NF-κB signaling pathway, resulting in anti-inflammatory effects and protection of lung microvascular barrier function [160]. In murine models of acute respiratory distress syndrome and sepsis, Dex@GNPs with natural glycyrrhizin protein nanoparticles can remodel the disorganized immune microenvironment and reduce tissue damage, presenting an effective method for localized anti-inflammatory and immunity regulation [161]. Dragon's blood pigment, a CMPK2 blocker, may be therapeutically effective in sepsis by regulating metabolic and signaling pathways [162]. Enoxolone-mediated sepsis suppression involving the NF-κB pathway and MEK/ERK signaling pathways suggests a new therapeutic approach that combines precise control of cellular signal transduction with anti-inflammatory treatment strategies [163]. Furthermore, miR-223 overexpression in macrophages hinders their polarization toward the M1 phenotype after LPS stimulation and decreases sepsis severity in the context of IL-4 pretreatment. These findings provide new insight into the induction of anti-inflammatory macrophages via regulation of cellular energy metabolism and provide a basis for macrophage-based cell therapy in sepsis [144].

The balance between immune activation and immunosuppression also depends on the pathogenesis of sepsis, and immunomodulation is the main therapeutic direction in infected patients. Here, recent major treatment strategies for sepsis are systematically characterized: immune checkpoint blockade, cellular and cytokine interventions, and targeted drug-delivery systems in **Figure 2**. In particular, PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors reverse immunosuppression and restore T cell effector function; thymosin α1 and cell-based products enhance host immune defense; GM-CSF and IFN-γ alleviate immune paralysis; and the modulation of macrophage M1/M2 polarization via pharmacological agents or nanoparticle delivery systems is involved in the precision treatment of the inflammatory response. Collectively, these strategies achieve targeted regulation of key nodes within the inflammatory network, suppressing excessive inflammation while preserving host defense mechanisms and multiorgan homeostasis, thereby providing novel theoretical frameworks and practical pathways for multi-level, controllable intervention in sepsis. While novel immunomodulatory therapies (melittin, GDF15, NWG, 4-OI, and nanoparticle-mediated delivery systems) show great promise in animal models of sepsis/sepsis-associated encephalopathy as well as in their in vitro counterpart, there is still a lack of clinical validation in patients, and few have been validated in national cohort studies with large sample sizes suggesting high specific efficacy. Specifically, the diagnostic value of GDF15 and its potential as a therapeutic target in sepsis-associated encephalopathy merit further experimental and clinical studies [164]. Furthermore, safety issues, dose optimization, pharmacokinetics, and patient heterogeneity require thorough evaluation in well-designed clinical trials. As such, these approaches should currently be considered promising therapeutic candidates rather than established clinical options.

6 DISCUSSION

This review comprehensively demonstrates the complex network properties of sepsis and the cytokine storm, including immune hyperactivation, cytokine networks, intercellular signaling crosstalk, microcirculatory dysfunction, metabolic remodeling, and multimodal cell death, revealing their multidirectional pathological mechanisms. As the core mechanism, the cytokine storm not only accelerates multiple organ dysfunction but also further promotes immune imbalance through a positive-feedback mechanism, thereby limiting the effectiveness of single-target interventions. Inhibition of the expression or activity of DNA-PKcs may be a promising strategy for treating sepsis, as it may inhibit or mitigate mitochondrial dysfunction and organ damage in sepsis-related MODS.

Current treatment for sepsis is mainly limited to anti-infective therapy, fluid resuscitation, and organ support. However, these strategies focus one-sidedly on the symptoms and complications of the disease, which is insufficient to regulate the complicated inflammatory process. The pathophysiology of sepsis

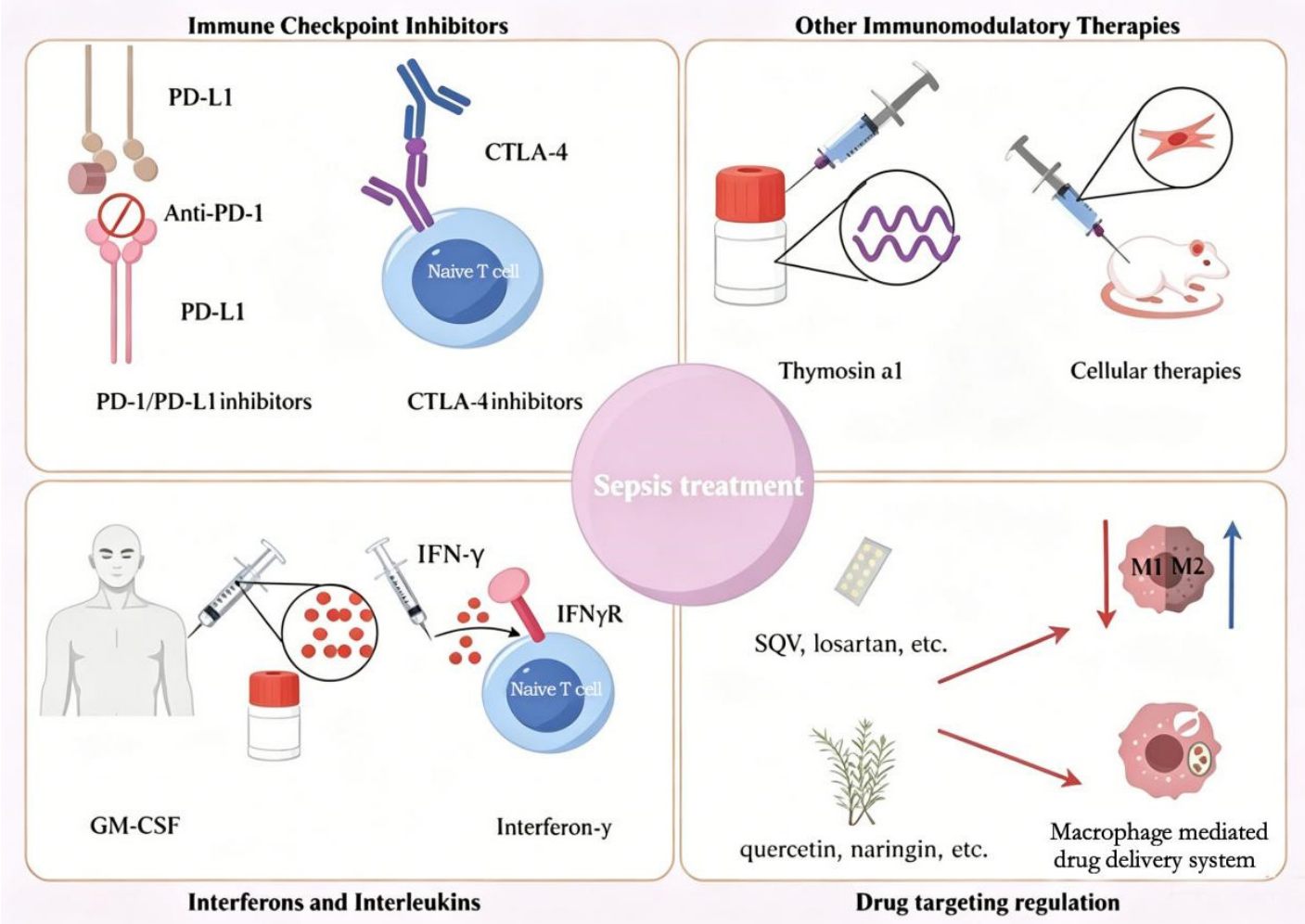

Figure 2. Immunomodulation and targeted intervention in sepsis. This figure shows the main immunomodulatory and targeted therapy strategies for treating sepsis. Anti-PD-1/PD-L1 and CTLA-4 blocking antibodies, as immune checkpoint inhibitors, can restore T cell function and ameliorate post-septic immunosuppression. Other immunomodulatory treatments, such as thymosin α1 or cellular therapy, also improve host immune defense and tissue recovery. Interferons and interleukins, such as GM-CSF and IFN-γ, promote immune cell activation and alleviate immune dysfunction. In drug-targeted regulatory strategies, the use of pharmacological agents (such as SQV, losartan, and quercetin), naringin, or macrophage-based drug delivery systems to regulate the balance between M1/M2 polarization can fine-tune the induction of inflammatory responses and favor the resolution of immune homeostasis re-establishment.

consists of signaling networks and metabolic systems interacting at multiple levels, and its nonlinear and dynamic nature suggests that single interventions may be insufficient to entirely suppress inflammatory cascades or return the immune system to homeostasis. Thus, multi-target and controllable interventions have been considered an important future direction. For instance, 4-OI has multi-target protective effects on LPS-induced septic AKI by inhibiting the inflammatory response and oxidative stress as well as promoting mitophagy [165].

Biomarkers and precision medicine hold promise in sepsis care. Early identification of high-risk patients, dynamic tracking of inflammation status, and incorporation of combined features of cytokine signatures, immune cell function, and metabolism may open options for stratified interventions and provide a support system for precise clinical decisions. The presence of different sepsis subphenotypes, as well as their relationship to disease trajectory, clinical presentations, and outcomes, has been identified through large-scale proteomics studies, leading the way to new biomarkers and precision-based interventions.

New immunomodulatory agents and anti-inflammatory interventions also offer intriguing treatment options for sepsis. For example, NAD(H)-loaded nanoparticles can enhance energy supply and inhibit inflammation, as well as promote immune homeostasis and vascular function [166]. Obeticholic acid also suppresses pro-inflammatory mediator synthesis and mitochondrial damage by reducing oxidative stress through inhibition of the NF-κB/NLRP3 signaling pathway [167]. Taken

together, these results argue for a paradigm shift in sepsis therapy, incorporating multi-level, dynamically controlled network intervention paradigms and moving away from rigid single-target approaches.

However, translational efforts and clinical practice still encounter several difficulties, such as the large heterogeneity of inflammatory networks, individual variability in immunological responses, and limitations of existing biomarkers. Notably, the combination of high-throughput omics technologies, single-cell analyses, and AI-based predictive models is anticipated to enhance early risk stratification and precision intervention, as well as to provide a theoretical basis for multi-target combination therapies [168]. Importantly, a study that utilized the Surviving Sepsis Campaign guidelines and applied machine learning to integrate six major treatments—including antibacterial therapy, balanced crystalloids, insulin therapy, corticosteroids, vasopressin, and bicarbonate—into a bundled algorithm, which significantly decreased 28-day mortality in patients with sepsis and septic shock. These findings indicate that, in the future, improving outcomes will be achieved predominantly through integrating network-based multidimensional interventions with precision medicine strategies.

ABBREVIATIONS

4-OI, 4-octyl itaconate; AKI, acute kidney injury; ALI, acute lung injury; ASC, apoptosis-associated speck-like protein containing a CARD; BMP9, bone morphogenetic protein 9; COX-2, cyclooxygenase-2; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; EV, extracellular vesicle; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSDMD, gasdermin D; IDO1, indoleamine 2,3-dioxygenase 1; LPS, lipopolysaccharide; Mac-1, macrophage-1 antigen; MAPK, mitogen-activated protein kinase; MDSC, myeloid-derived suppressor cell; MODS, multiple organ dysfunction syndrome; MyD88, myeloid differentiation primary response 88; NET, neutrophil extracellular trap; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, nitric oxide; NWG, N-(1,3,4-oxadiazol-2-yl) guanidine; PTX3, pentraxin 3; SOFA, sequential organ failure assessment; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TLR, Toll-like receptor; Treg, regulatory T cell.

DECLARATIONS

Author contributions

Linzhu Li and Kaikai Wang contributed equally to this work and share first authorship. Linzhu Li and Kaikai Wang were responsible for literature retrieval and manuscript drafting. Yongbo Li participated in the design of the article framework and manuscript revision. Wenrong Zhang, Jianlong Ma, and Wenzhi Zhang were responsible for literature screening, summarizing research progress, and content organization. Wanquan Guo and Qianqian Zhang participated in literature analysis, figure design, and language polishing. Zhijing Song was responsible for the overall study design, academic supervision, manuscript review, and final approval of the manuscript. All authors have read and approved the final version of the manuscript.

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