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Post-translational modifications in sepsis: Mechanistic insights and therapeutic opportunities

Wenyue Gao[1,2,3,4], Yue Zhang[1,2,3], and Liuluan Zhu[1,2,3]*

[1]Beijing Key Laboratory of Emerging Infectious Diseases, Institute of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China

[2]Beijing Institute of Infectious Diseases, Beijing, China

[3]National Center for Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing, China

[4]Department of Infectious, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, China

Abstract

Sepsis, a life-threatening condition marked by systemic inflammation and multi-organ dysfunction, poses a persistent clinical challenge. Post-translational modifications (PTMs) dynamically regulated inflammatory signaling, immune responses, and cell death, positioning them as a pivotal focus in sepsis research. This review systematically explores the regulatory networks of five key PTMs – phosphorylation, ubiquitination, SUMOylation, acetylation, and lactylation – in sepsis. In this review, we highlight recent discoveries of genes and molecules that modulate these PTMs, influencing inflammation and organ dysfunction, and evaluate their potential as therapeutic targets or prognostic biomarkers. Furthermore, we discuss how PTMs offer novel therapeutic opportunities, providing novel insights to address the shortcomings of traditional anti-infective approaches.

Keywords: Sepsis; Post-translational modifications; Phosphorylation; Ubiquitination; SUMOylation; Acetylation; Lactylation; Inflammation

***Corresponding author:**
Liuluan Zhu
(zhuliuluan@ccmu.edu.cn)

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1. Introduction

Sepsis arises from a dysregulated host response to infection, resulting in systemic inflammation and multiple organ dysfunctions.[1] Complications such as acute kidney injury (AKI), acute lung injury (ALI), and myocardial injury are frequent and severe, contributing to elevated morbidity and mortality rates.[2-4] Despite progress in anti-infective therapies and organ support, the intricate pathogenesis of sepsis continues to hinder effective clinical management.

In eukaryotes, protein function is diversified through post-translational modifications (PTMs), which dynamically regulate cellular processes.[5] Increasingly, PTMs have been recognized as central regulators of sepsis progression, modulating inflammatory signaling, immune cell polarization, and programmed cell death.[6] This review examines five major PTMs – phosphorylation, ubiquitination, SUMOylation, acetylation, and lactylation, an emerging form of modification – focusing on their roles in sepsis, and

explores their potential as biomarkers and therapeutic targets to enhance sepsis treatment enhance.

2. Host response dysregulation in sepsis

Sepsis arises from a dysregulated host immune response, characterized by a vicious cycle of hyperinflammation, immunosuppression, coagulation abnormalities, and metabolic dysregulation. This cascade disrupts immune homeostasis, driving complex molecular interactions that culminate in multi-organ dysfunction.

In the early phase of sepsis, pathogen-associated molecular patterns and damage-associated molecular patterns engage pattern recognition receptors, such as toll-like receptors (TLRs), on immune cells. This interaction activates signaling cascades, including nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, triggering a surge of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and interleukin 1 beta (IL-1β).[7] Concurrently, excessive activation of the complement system (*e.g.*, C3a, C5a) and the formation of neutrophil extracellular traps further amplify inflammation, damaging vascular endothelium, causing capillary leakage and tissue edema.[8,9] These processes exacerbate tissue injury and set the stage for systemic complications.

Following the initial inflammatory storm, the host immune system often transitions into a compensatory anti-inflammatory response syndrome. During this phase, pro-inflammatory cytokine production declines, while anti-inflammatory mediators (*e.g.*, IL-10, transforming growth factor beta) are overexpressed, suppressing immune cell function.[10] This shift is accompanied by widespread apoptosis of T cells and B cells, impaired antigen-presenting capacity of dendritic cells, and expansion of myeloid-derived suppressor cells. In addition, upregulation of immune checkpoint molecules (*e.g.*, programmed cell death protein 1 [PD-1], cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) on T cell surfaces induces T cell exhaustion.[11] This immunosuppressive state increases susceptibility to secondary infections, impairs pathogen clearance, and significantly increases mortality risk.

Dysregulated coagulation forms a positive feedback loop with inflammation, exacerbating sepsis pathology. Inflammatory cytokines inhibit the thrombomodulin-protein C system, impairing anticoagulation while upregulating tissue factor expression to activate the extrinsic coagulation pathway. Simultaneously, increased levels of plasminogen activator inhibitor-1 suppress fibrinolysis, promoting platelet activation and fibrin deposition.[12,13] These changes lead to microthrombi formation, compounded by complement activation products that further damage the endothelium and enhance platelet aggregation. The resulting disseminated intravascular coagulation disrupts organ microcirculation, causing ischemic injury and worsening multi-organ failure.[14]

Metabolic reprogramming is a hallmark of sepsis, driven by inflammatory signals that shift immune cell metabolism toward glycolysis, leading to lactate accumulation and metabolic acidosis.[15] Excessive reactive oxygen species (ROS) induces mitochondrial dysfunction, while lipid peroxidation promotes ferroptosis, a form of programmed cell death. These processes impair immune cell function and contribute to multi-organ metabolic failure.[16,17] Together, these metabolic disruptions exacerbate the systemic effects of sepsis and hinder recovery.

PTMs intricately regulate these dysregulated host responses, serving as critical molecular switches in sepsis pathogenesis. For instance, phosphorylation of NF-κB modulates excessive inflammation,[18] while phosphorylation of lymphocyte-specific protein-1 (Lsp1) triggers B cell apoptosis.[19] In addition, the E3 ubiquitin ligase TRIM47 promotes TNF-α-induced endothelial cell activation through ubiquitination,[20] and lactate-mediated lactylation of mitochondrial fission protein 1 (Fis1) drives mitochondrial dysfunction.[21] These PTM-mediated mechanisms, detailed in subsequent sections, highlight potential therapeutic targets for mitigating sepsis-induced organ damage.

3. Phosphorylation and sepsis

Protein phosphorylation, the earliest discovered PTM, is a well-studied mechanism in sepsis. It involves the kinase-mediated transfer of a phosphate group from ATP to specific amino acid residues,[6] regulating cellular signaling, metabolism, and inflammation.[22] In sepsis, phosphorylation modulates key pathways – such as NF-κB, MAPK, STAT3, and PI3K/ATK – affecting inflammation, immunity, and apoptosis, and thus influencing disease progression and outcomes.

3.1. NF-κB signaling pathway

NF-κB, a pivotal transcription factor in immune and inflammatory responses, comprises five subunits: p50, p52, RelA (p65), c-Rel, and RelB.[23] In resting cells, NF-κB is sequestered in the cytoplasm by its inhibitor, IκB.[24] Activation proceeds through two distinct pathways: classical and non-classical.[25]

The classical pathway, initiated by inflammatory cytokines, involves IKK complex-mediated phosphorylation and subsequent degradation of IκB, releasing NF-κB dimers (*e.g.*, p50/p65), which translocate

to the nucleus and drive pro-inflammatory gene transcription.[23] TNF-α-induced protein 8-like 2 (TIPE2) and echinatin (Ecn) inhibit p65 nuclear translocation, reducing inflammation and damage in sepsis.[26,27] In contrast, the microRNA-210 host gene (MIR210HG) enhances IκBα phosphorylation and p65 nuclear translocation, exacerbating sepsis-associated AKI.[18] In addition, p65 phosphorylation is a critical regulatory step; transcription factor Kruppel-like factor 13 (KLF13) and astragaloside IV (AST) suppress p65 phosphorylation, mitigating sepsis-related myocardial injury and inflammation,[28,29] whereas transcription coactivator PPARG coactivator 1 alpha (PGC-1α) promotes it, enhancing cytokine release and inhibiting cardiomyocyte apoptosis.[30] Parkinson's disease protein 7 (PARK7) protects against sepsis-induced AKI by simultaneously blocking p65 nuclear translocation and phosphorylation.[31]

The non-classical pathway is typically activated by specific stimuli, this pathway involves phosphorylation of p100, its processing to p52, and subsequently dimerization with RelB for nuclear translocation and target gene transcription.[23] SHP-1, a protein tyrosine phosphatase, inhibits this pathway by suppressing p52 phosphorylation and nuclear translocation, dampening hyperinflammation and ALI in sepsis. SHP-1 also negatively regulates the classical pathway by inhibiting the p50 phosphorylation and reducing p65 transcription and translation.[31]

Targeting dysregulated NF-κB signaling through molecules such as TIPE2, MIR210HG, KLF13, and SHP-1, alongside bioactive compounds such as Ecn and AST, offers promising anti-inflammatory strategies for sepsis management.

3.2. MAPK signaling pathway

MAPKs, a family of serine/threonine kinases, regulate proliferation, apoptosis, and inflammation, playing a pivotal role in sepsis pathogenesis through aberrant activation and subsequent overproduction of pro-inflammatory cytokines.[32] The MAPK signaling pathway encompasses four primary cascades: extracellular signal-regulated kinase (ERK) 1/2, c-Jun N-terminal kinase (JNK), p38, and ERK5. These cascades are phosphorylated and activated by upstream MAPK kinases to modulate downstream targets.[33] In sepsis, ERK1/2, JNK, and p38 are the most extensively studied subtypes, with their activation intricately linked to the inflammatory response and disease progression.

ERK1/2 is primarily activated by growth factors (*e.g.*, epidermal growth factor) and inflammatory signals (*e.g.*, TLR4) stimulation. Upon activation, ERK1/2 phosphorylates transcription factor c-Fos, promoting the expression of pro-inflammatory cytokines, including IL-1β and IL-6.[34] Beyond inflammation, ERK1/2 supports adaptive immunity by regulating cell proliferation and inhibiting apoptosis through the mitochondrial pathway. This sustains T and B cell survival, enhancing host defense against infection.[35,36] For instance, adrenomedullin 2 (ADM2) stimulates ERK1/2 phosphorylation, promoting T and B cell proliferation and bolstering anti-infective immunity.[37] Similarly, artesunate enhances ERK1/2 phosphorylation in $CD4^+$ and $CD8^+$ T cells, reducing apoptosis and mitigating sepsis-induced immunosuppression.[38]

JNK, activated by stress signals such as oxidative stress and pro-inflammatory cytokines, phosphorylates c-Jun and facilitates activating transcription factor 4 (ATF4) nuclear translocation. These events drive the transcription of inflammatory genes, amplifying the inflammatory response in sepsis.[39] JNK's role in exacerbating inflammation makes it a critical target for therapeutic intervention.

Several compounds have shown promise in modulating ERK1/2 and JNK activity to attenuate sepsis-induced inflammation. Tetrahydrocurcumin (THC) inhibits phosphorylation of both JNK and ERK1/2, reducing pro-inflammatory cytokine production and improving cardiac function in sepsis models.[40] Similarly, pinaverium bromide (PVB) suppresses ERK1/2 and JNK phosphorylation in neutrophils by decreasing ROS production. This attenuates inflammatory factor production and mitigates early-stage sepsis-induced inflammation. In addition, PVB inhibits phosphorylation of IκBα and p65, key components of NF-κB signaling pathway, further reducing pro-inflammatory responses in neutrophils.[41] These findings highlight the therapeutic potential of targeting MAPK pathways to balance inflammatory and immune responses in sepsis.

MAPK p38 drives inflammatory factor expression by phosphorylating transcription factors such as ATF2 and C/EBP homologous protein (CHOP).[42] It also directly regulates NLRP3 inflammasome assembly, promoting IL-1β/IL-18 maturation and release. Anti-inflammatory mediators such as maresin-1 (MaR1) and fisetin suppress p38 MAPK phosphorylation, decreasing pro-inflammatory factor expression and alleviating sepsis-induced organ damage.[43,44] Peptide-proline isomerase Pin1 enhances NLRP3 inflammasome transcription and activation through p38 MAPK phosphorylation, amplifying the inflammatory response and exacerbating organ damage in sepsis.[45] Furthermore, p38 MAPK enhances the activity of caspase-1, promoting gasdermin D cleavage and inducing pyroptosis.[46] In the pathogenesis of sepsis-associated AKI, the TLR4/MyD88 signaling pathway promotes p38 MAPK

phosphorylation, exacerbating renal tubular epithelial cell pyroptosis,[47] while the endogenous regulator Wild-type p53-induced phosphatase 1 (WIP1) exerts a negative regulatory effect by dephosphorylating p38 MAPK, alleviating pyroptosis-related kidney injury.[48]

Thus, targeting the MAPK pathway offers promising avenues for suppressing inflammation and balancing immune responses. Its interactions with NF-κB, the NLRP3 inflammasome, and cell death pathways demonstrate its potential in treating sepsis. Molecules such as ADM2, MaR1, peptidyl-prolyl cis/trans isomerase (Pin1), WIP1, and TLR4 provide opportunities for precise intervention by modulating MAPK phosphorylation. Natural products and synthetic compounds, including THC, PVB, artesunate, and fisetin, exhibit therapeutic potential by improving organ function and survival rates through multi-target effects.

3.3. Signal transducer and activator of transcription 3 (STAT3) signaling pathway

STAT3, a member of the STAT protein family, is a central transcription factor in immune and inflammatory signaling.[49] Following phosphorylation, STAT3 translocates to the nucleus, driving transcription of genes involved in inflammation, cell proliferation, differentiation, and apoptosis during the acute phase of sepsis, thereby modulating immune responses and multi-organ dysfunction.[50,51]

Colchicine inhibits NLRP3 inflammasome activation by suppressing STAT3 phosphorylation, reducing inflammation, pyroptosis, and oxidative stress in sepsis-induced ALI.[52] Conversely, phospholipase D2 (PLD2) enhances STAT3 phosphorylation through phospholipid acid, negatively regulating tight junction protein expression in pulmonary vascular endothelium and exacerbating ALI.[53] In sepsis-associated AKI, Lyn (a Src family kinase) and pectolinarigenin (a flavonoid) suppress STAT3 phosphorylation, inhibiting inflammatory factor release and reducing renal cell apoptosis, thus protecting against AKI.[54,55] In addition, 4-octyl itaconate, a multi-target itaconate derivative, suppresses STAT3 phosphorylation to mitigate renal inflammation and oxidative stress while promoting mitophagy and cell homeostasis.[56] Mesenchymal stem cells regulate inflammatory response by inhibiting both STAT1 and STAT3 phosphorylation, modulating T helper (Th) cell subset numbers and functions, reducing organ damage, and improving survival in septic models.[57]

The pivotal role of STAT3 in sepsis highlights the need to develop therapies that downregulate its signaling. Newly identified regulators such as PLD2 and Lyn offer novel therapeutic targets, while colchicine, pectolinarigenin, 4-octyl itaconate, and mesenchymal stem cells show promise as STAT3-targeting agents in sepsis management.

3.4. PI3K/AKT signaling pathway

The PI3K/AKT pathway is a vital intracellular signaling network wherein phosphatidylinositol 3-kinase (PI3K) activates AKT through phosphorylation.[58] Activated AKT regulates inflammation, oxidative stress, and apoptosis by influencing downstream effectors.[59]

Targeted modulation of the PI3K/AKT pathway can mitigate sepsis-induced organ damage by balancing inflammation and tissue repair. Blocking hepatocyte growth factor binding to c-Met inhibits PI3K/AKT phosphorylation, reducing oxidative stress, pro-inflammatory cytokine production (*e.g.*, IL-6), and cardiomyocyte apoptosis in early sepsis, though prolonged inhibition may impair tissue regeneration.[60,61] Alternatively, inhibiting sphingosine 1-phosphate lyase (S1P) and activating S1P receptor type 3 suppress AKT phosphorylation, preserving lung and kidney microvascular barriers and reducing systemic inflammation, offering potential for antibiotic-resistant cases.[62] AKT-driven NF-κB phosphorylation amplifies pro-inflammatory cascades, but compounds such as annexin A1 (Ac2-26) and hibifolin inhibit NF-κB, protecting against renal and lung injury.[63-65] In contrast, the traditional Chinese medicine compound Xuebijing (XBJ) activates AKT phosphorylation by increasing vascular endothelial growth factor A expression to improve intestinal microcirculation in sepsis.[66] Similarly, phenylpropylene (BNP) exerts anti-inflammatory effects by inducing AKT phosphorylation and reducing IL-6 expression.[67]

The dual role of the PI3K/AKT pathway in sepsis – both protective and detrimental – complicates its therapeutic application. Nevertheless, hibifolin, XBJ, and phenpropylline merit further exploration as potential sepsis treatments.

4. Ubiquitination and sepsis

Ubiquitination, mediated by E1-E2-E3 cascades, critically regulates immune responses and cell death in sepsis.[68] This process involves the attachment of ubiquitin, a 76-amino acid protein with seven lysine residues (K6, K11, K27, K29, K33, K48, K63), to substrate proteins, forming monomeric, branched and linear chains.[69] E3 ubiquitin ligases, categorized into RING, HECT, and RBR families, confer substrate specificity.[70] Ubiquitination modification plays a key role in modulating NLRP3 inflammasome activation and programmed cell death pathways, influencing sepsis pathogenesis.

4.1. NLRP3 inflammasome

The NLRP3 inflammasome, a multiprotein complex, is crucially regulated by ubiquitination in terms of its degradation or activation.[71,72] RING-type E3 ligases Cbl-b and RNF125 prevent sepsis by targeting NLRP3 for K63- and K48-linked polyubiquitination, inhibiting NLRP3 inflammasome activation.[73] β-TrCP1, another E3 ubiquitin ligase, promotes NLRP3 degradation through K27-linked ubiquitination, while the transcriptional coactivator yes-associated protein (YAP) stabilizes NLRP3 by blocking its interaction with β-TrCP1.[74] Conversely, the cullin-RING-type E3 ligase KBTBD7 promotes NLRP3 activation and pro-inflammatory factors release by ubiquitinating and degrading the transcription factor KLF15, exacerbating brain injury in sepsis.[75] Furthermore, heat shock protein family A member 8 (HSPA8) inhibition promotes the E3 ligase SKP2 degradation, attenuating NLRP3 ubiquitination, thereby exacerbating pyroptosis and sepsis-induced ALI.[76] Tissue inhibitor of metalloproteinase 2 (TIMP2) exerts a renoprotective role in sepsis-associated AKI by enhancing the E3 ligase MARCH7-mediated NLRP3 ubiquitination degradation and attenuating downstream pyroptosis.[77]

These findings highlight the therapeutic potential of targeting NLRP3 ubiquitination in sepsis. Newly identified regulators such as YAP, KLF15, HSPA8, and TIMP2 offer novel avenues for therapeutic intervention by modulating NLRP3 degradation and activation.

4.2. Programmed cell death

Sepsis induces programmed cell death, a process dynamically regulated by ubiquitination.[78] RING-type E3 ligase FBXW7 promotes alveolar epithelial cells ferroptosis and aggravates sepsis-induced ALI by mediating AUF1 ubiquitination and degradation.[79] Conversely, HECT-type E3 ligase WWP2 inhibits oxidative stress and ferroptosis in cardiomyocytes by promoting long-chain acyl CoA synthetase 4 (FACL4) ubiquitination, improving myocardial injury and cardiac function in sepsis.[80] In pyroptosis regulation, CHIP (a chaperone-dependent E3 ligase) inhibits NLRP3 activation and pyroptosis by promoting KPNA2 poly-ubiquitination, thus alleviating sepsis-induced cardiac dysfunction.[81] YL-109, a small molecule compound that upregulated CHIP expression, demonstrates therapeutic potential by inhibiting this pathway in various tissues, improving septic multi-organ damage.[82] Similarly, samotolisib, the PI3K/mTOR pathway inhibitor, activates HECT-type E3 ligase Nedd4, inducing caspase-11 ubiquitination, thereby specifically blocking hepatocyte pyroptosis and improving ALI in sepsis.[83] The TRIM family, a RING-type E3 ligases subfamily,[70] exhibits dual role of cell death regulation in sepsis. TRIM21 mediates OAS3 K48-linked polyubiquitination in lung epithelial cells, inhibiting apoptosis, thus attenuating sepsis-induced ALI.[84] It also promotes interferon regulatory factor 1 (IRF1) ubiquitination, reducing IRF1 enrichment, further improving sepsis-induced ALI.[85] However, TRIM31 activates the NF-κB pathway by binding to TAK1 and enhancing its ubiquitination, inducing cardiomyocyte apoptosis and a "pro-injury" phenotype in sepsis.[85]

These findings highlight the therapeutic potential of modulating E3 ligase networks – particularly through small-molecule compounds such as YL-109 and samotolisib – to reprogram programmed cell death pathways and improve sepsis outcomes.

5. SUMOylation and sepsis

Small ubiquitin-like modifier (SUMO), a protein containing ~100 amino acids, is covalently attached to lysine residues of target proteins through a three-step enzymatic cascade mediated by E1, E2 (UBC9), and E3 ligases.[86] This process, known as SUMOylation, participates in regulating diverse biological processes, including cell signaling, gene transcription, cell proliferation, and apoptosis.[87]

In sepsis, SUMOylation plays a critical role in modulating inflammation and immune homeostasis. Ubiquitin-conjugating enzyme 9 (UBC9), the sole E2 ligase for SUMOylation, its deficiency leads to dendritic cell hypermaturation, aberrant release of IL-18/IL-1β and enhances T cell activation, increasing mortality in septic mice by enhancing, which indicating a protective role for SUMOylation in suppressing excessive inflammation.[88] SUMO can competitively bind to the same site on IκBα as ubiquitin, inhibiting its ubiquitination and degradation, thus blocking NF-κB nuclear translocation and downstream pro-inflammatory factor transcription.[86] SUMOylation deficiency abolishes this inhibition, resulting in abnormal NF-κB-dependent inflammatory factors and type I interferon secretion, potentially by regulating interferon-β (Ifnb1) expression and suppressing unanticipated amplification of TLR signaling.[87] Macrophages are important immune cells, with a significant impact on immune homeostasis and inflammatory processes in sepsis.[89] SUMO-specific protease 1 (SENP1) regulates transcription factor KLF4 activity through deSUMOylation. As a key regulator of macrophage polarization, KLF4 upon SENP1-mediated deSUMOylation enhances NF-κB signaling, driving M1 macrophage polarization and exacerbating inflammation.[90] SENP1 also promotes Sp3 expression through deSUMOylation and interaction with NF-κB,

enhancing lipopolysaccharide-induced macrophage inflammation.[91] Conversely, ginkgolic acid inhibits SUMOyation, promoting NF-κB p65 phosphorylation and nuclear translocation, increasing the release of macrophage inflammatory factors and apoptosis, thereby exacerbating sepsis-induced organ damage.[92]

In summary, SUMOylation exerts an anti-inflammatory and protective role in sepsis by stabilizing IκBα to inhibit NF-κB signaling, regulating macrophage polarization, inflammatory responses, and cell apoptosis. The dynamic balance of the core regulatory nodes UBC9 and SENP1 profoundly impacts disease progression, suggesting that targeting UBC9 and SENP1 may offer novel sepsis treatments.

6. Acetylation and sepsis

Acetylation, a PTM catalyzed by acetyltransferase, modulates gene expression and participates in cellular processes, including gene transcription and signal transduction.[5] Aberrant acetylation within the TLR4 signaling complex is implicated in dysregulated immune responses, suggesting acetylation as a potential therapeutic target in sepsis.[93]

Table 1. Roles of regulatory factors involved in different PTMs and the corresponding targets in sepsis

Targets	Regulatory factors	Impact on sepsis	References
Phosphorylation			
NF-κB	MIR210HG, PGC-1α	Promote	18,30
	TIPE2, Ecn, KLF13, AST, PARK7, SHP-1, PVB	Inhibit	26-29,31,41
MAPK	Pin1, TLR4	Promote	45,47
	THC, PVB, ADM2, artesunate, MaR1, fisetin, WIP1	Inhibit	37,38,40,41,43,44,48
STAT3	PLD2	Promote	53
	Lyn, PEC, colchicine, 4-OI, MSCs	Inhibit	52,54-57
PI3K/ATK	HGF, S1P	Promote	60,62
	S1PR3, Ac2-26, Hibifolin, XBJ, BNP	Inhibit	62,64-67
Ubiquitination			
NLRP3	Cbl-b, RNF125, β-TrCP1, TIMP2	Promote	73,74,77
	YAP, KBTBD7, HSPA8	Inhibit	74-76
Other target	FBXW7	Promote	79
	WWP2, CHIP, YL-109, samotolisib	Inhibit	80-83
SUMOylation			
NF-κB	SENP1, GA	Promote	91,92
	UBC9, KLF4	Inhibit	88,90
Acetylation			
SIRTs	GITR	Promote	99
	GAS5, AVS, NMN, MK-4, Zn^{2+}	Inhibit	95-97,101,102
Lactylation			
Histone	METTL3, EGR1, RhoA	Promote	105-107
Non-histone	Fis1, HMGB1	Promote	21,109
	PDHA1	Inhibit	21

Abbreviations: Ac2-26: Annexin A1; ADM2: Adrenomedullin 2; AST: Astragaloside IV; AVS: Nicaraven; BNP: Phenpropylline; Cb1-b: Casitas B-lineage lymphoma proto-oncogene b; Ecn: Echinatin; EGR1: Early growth response protein 1; Fis1: Mitochondrial fission protein 1; GA: Ginkgolic acid; GAS5: Growth arrest-specific transcript 5; GITR: Glucocorticoid-induced TNFR-related protein; HGF: Hepatocyte growth factor; HMGB1: High mobility group box 1; HSPA8: Heat shock protein family A member 8; KLF: Kruppel-like factor; MaR1: Maresin-1; MIR210HG: MicroRNA-210 host gene; MK-4: Menadione 4; MSCs: Mesenchymal stem cells; NMN: Nicotinamide mononucleotide; 4-OI: 4-Octyl itaconate; PARK7: Parkinson's disease protein 7; PDHA1: Pyruvate dehydrogenase E1 component subunit α; PEC: Pectolinarigenin; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; Pin1: Peptidyl-prolyl cis/trans isomerase; PLD2: Phospholipase D2; PVB: Pinaverium bromide; S1P: Sphingosine 1-phosphate lyase; S1PR3: S1P receptor type 3; SENP1: SUMO-specific peptidase 1; SHP-1: Src homology region 2 domain-containing phosphatase-1; THC: Tetrahydrocurcumin; TIMP2: Tissue inhibitor of metalloproteinase 2; TIPE2: TNF-α-induced protein 8-like 2; TLR4: Toll-like receptor 4; β-TrCP1: Beta-transducin repeats-containing protein 1; UBC9: Ubiquitin-conjugating enzyme 9; WIP1: Wild-type p53-induced phosphatase 1; XBJ: Xuebijing; YAP: Yes-associated protein.

Sirtuins (SIRTs), a family of nicotinamide adenine dinucleotide (NAD)-dependent deacetylases (SIRT1-7), exhibit antioxidant, anti-apoptotic, and anti-inflammatory properties, positioning them as key regulators in sepsis.[94] Specifically, SIRT1 activation, mediated by growth arrest-specific transcript 5 (GAS5), nicaraven (AVS), and nicotinamide mononucleotide (NMN), attenuates inflammation by inhibiting high mobility group box 1 (HMGB1) and NF-κB p65 acetylation, respectively, thereby improving survival and mitigating organ damage in sepsis models.[95-97] NMN also inhibits NF-κB p65 phosphorylation, thereby preventing sepsis-induced ALI.[97]

SIRT2 is a negative regulatory factor of autophagy. Its inhibition promotes autophagy and attenuates septic AKI through increasing FOXO1 acetylation.[98] Furthermore, the costimulatory molecule glucocorticoid-induced TNFR-related protein (GITR) induces SIRT2 degradation by recruiting E3 ligase MARCH7, reducing NLRP3 ubiquitination but increasing its acetylation, thereby exacerbating macrophage pyroptosis, and systemic inflammatory injury.[99] SIRT3, localized in the mitochondrial matrix,[100] mitigates oxidative stress and inflammation in sepsis-induced ALI by inhibiting p53 acetylation, an effect enhanced by menadione 4 (MK-4).[101] SIRT7 (the only sirtuin located in the nucleolus) is required for ribosomal DNA transcription.[100] SIRT7 inactivation by Zn^{2+} increases parkin acetylation, promoting parkin-mediated mitophagy and inhibiting NLRP3 activation, thus ameliorating AKI in sepsis.[102]

SIRTs and acetylation critically regulate inflammation and sepsis progression, making them promising therapeutic targets. Molecules such as GAS5, AVS, NMN, GITR, MK-4, and Zn^{2+} may offer avenues for targeted intervention.

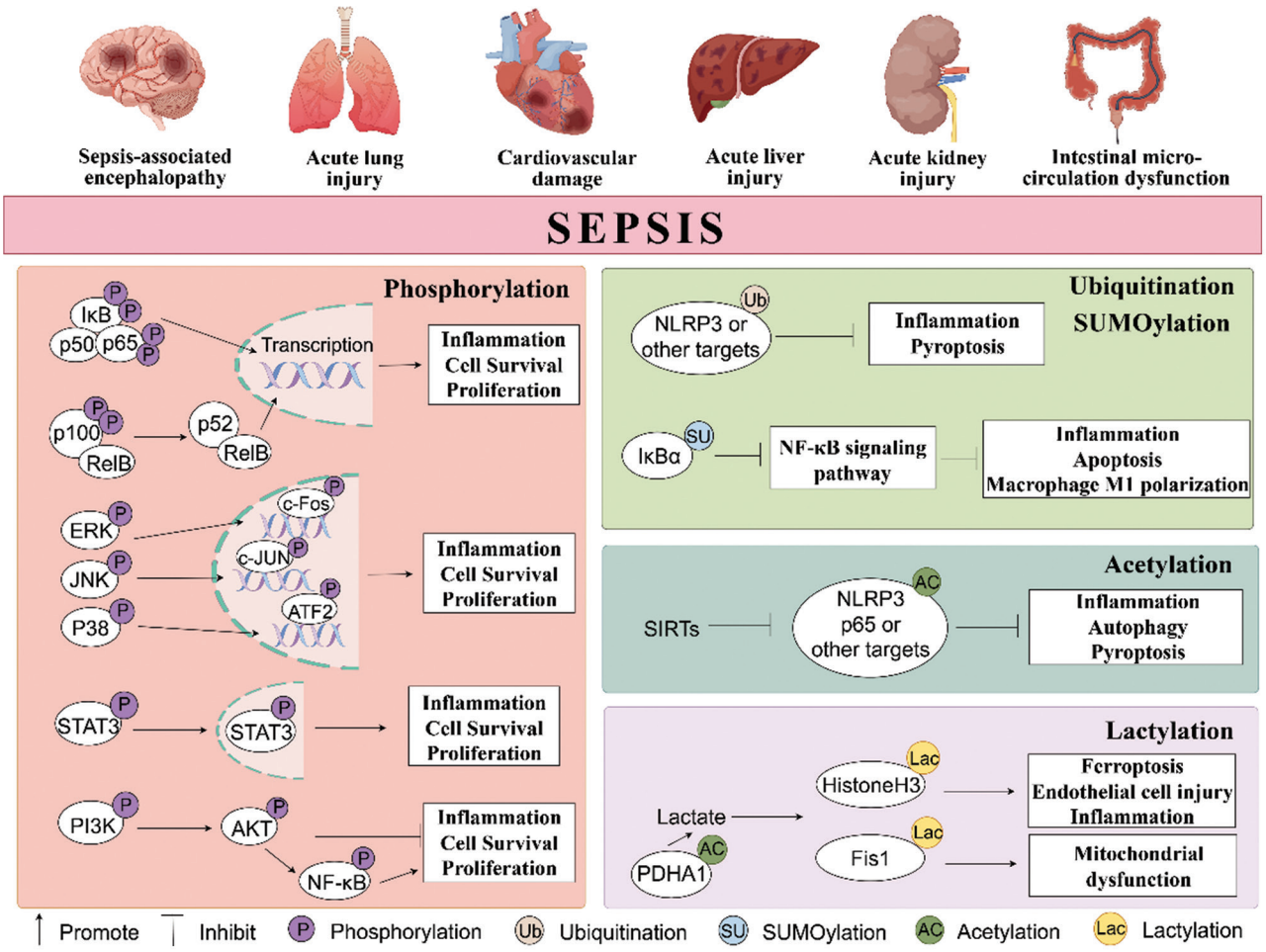

Figure 1. Overview of the regulatory mechanisms of post-translational modifications in sepsis. The main types of protein translation post-translational modifications involved in sepsis and multiple organ dysfunction syndrome are phosphorylation, ubiquitination, SUMOylation, acetylation, and lactylation. The schematic diagram was created on www.figdraw.com.

7. Lactylation and sepsis

Lactylation, the addition of lactyl groups to lysine residues, represents another PTM implicated in sepsis.[103] In sepsis, increased glycolysis leads to lactate accumulation, driving both histone and non-histone lactylation, thereby dynamically controlling gene expression and contributing to organ dysfunction.[104]

7.1. Histone lactylation

Histone H3 lysine 18 lactylation (H3K18la), a specific lactylation site, promotes METTL3 expression and transcription factor early growth response protein 1 (EGR1) enrichment, exacerbating ALI in sepsis.[105,106] Lactate-induced H3K18la activates RhoA protein and mediates downstream inflammation and apoptosis, leading to kidney injury. It also activates ezrin K263 lactylation, identifying ezrin as a lactate substrate for the 1st time.[107] Lactate also increases H3K14la levels, activating inflammation of endothelial cells and lung injury by promoting transcription of ferroptosis-related genes *TFRC* and *SLC40A1*.[108] These findings suggest histone lactylation as a regulator of sepsis-induced organ damage, with METTL3 and EGR1 represents promising therapeutic targets.

7.2. Non-histone lactylation

While initially identified on histones, non-histone lactylation is also a focus of current research. Lactate promotes HMGB1 lactylation and acetylation through a p300/CBP-dependent pathway, leading to its release and endothelial barrier dysfunction, promoting sepsis development.[109] In addition, lactate mediates mitochondrial fission 1 protein lysine 20 (Fis1 K20la) lactylation, promoting excessive mitochondrial fission and exacerbating sepsis-induced AKI. Notably, this process is driven by SIRT3 downregulation-mediated hyperacetylation and inactivation of pyruvate dehydrogenase E1 component subunit α (PDHA1), leading to lactate excess in endothelial cells of renal tubules.[21] The interplay between lactylation and acetylation, driven by lactate and acetyl-CoA, respectively, highlights the importance of metabolic homeostasis in sepsis.[110] Targeting HMGB1 and PDHA1 may offer novel therapeutic strategies by modulating the dynamic homeostasis between acetylation and lactylation.

8. Conclusion and perspectives

Sepsis pathogenesis involves an initial hyperinflammation phase driven by excessive inflammatory cytokines release, followed by immunosuppression characterized by anti-inflammatory cytokine production, immune cell death, and regulatory cell proliferation.[111] PTMs, critical regulators of protein function, are implicated in sepsis pathogenesis, offering potential therapeutic targets.[112]

This review summarizes the potential role of PTMs in sepsis and sepsis-induced multiple organ dysfunction identified in recent years (Figure 1 and Table 1). Phosphorylation, ubiquitination, and SUMOylation primarily contribute to the early inflammatory storm, with NF-κB, MAPK, and STAT3 phosphorylation driving pro-inflammatory cytokine release, and E3 ligase regulating NLRP3 inflammasome activation and cell death. The PI3K/AKT pathway exhibits dual role in sepsis. XBJ improves intestinal microcirculation by activating the PI3K/AKT pathway,[66] while hibifolin inhibits this pathway to alleviate lung injury,[65] highlighting the need for tissue-specific regulation. Acetylation and lactylation are dynamically regulated by metabolites (acetyl-CoA, lactate), forming a "metabolism–PTM-gene expression" cascade. SIRT3 downregulation-mediated PDHA1 acetylation induces Fis1 lactylation, suggesting that targeting metabolic enzymes may regulate multiple PTMs simultaneously.[21] Furthermore, NAD+ precursor NMN inhibits NF-κB by activating SIRT1, providing a strategy for combined metabolic and immune regulation.[97]

However, most studies are limited to single PTM or organ, lacking systematic analysis of multi-modification interactions like ubiquitination-acetylation competition, and systemic effects. Tissue-specific E3 ligase distribution, such as the opposing effects of TRIM21 in lung epithelium versus TRIM31 in myocardium, highlights the need for organ-targeted delivery systems, reducing off-target toxicity.[85,113] Future studies can focus on developing dual-function molecules such as inhibiting phosphorylation and activating deacetylation, synergistically regulating immune balance, or combining PTM inhibitors with drugs targeting various mechanisms to improve sepsis treatment efficacy.

In conclusion, exploring PTMs-related regulatory factors offers a novel strategy for developing sepsis therapeutics. However, translation to clinical application requires further investigation to shift sepsis treatment from "broad-spectrum anti-inflammation" to "precise modification and regulation."

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Conflict of interest

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Author contributions

Conceptualization: Wenyue Gao
Visualization: Wenyue Gao
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