

Autophagic Flux Blockade and Endoplasmic Reticulum Stress as Convergent Drivers of T Cell Apoptosis in Sepsis-Induced Immunosuppression

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Research Article

Keywords: sepsis, immunosuppression, T cell apoptosis, autophagic flux, endoplasmic reticulum stress, ER-phagy, mTOR, PIK3C3/VPS34, immune endotype, unfolded protein response

Posted Date: October 22nd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11255438/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background: Most deaths from sepsis now occur during the immunosuppressive phase rather than the initial cytokine storm, and apoptotic depletion of T lymphocytes is the cellular hallmark of this state. Yet the stress mechanisms that commit septic T cells to death remain split between two literatures: impaired autophagy and sustained endoplasmic reticulum stress.

Main body: This narrative review integrates the two pathways into a single interconnected stress network. In septic T cells, autophagic flux is blocked at both ends: hyperactivation of the mechanistic target of rapamycin (mTOR) suppresses the ULK1 initiation complex and the class III phosphoinositide 3-kinase PIK3C3/VPS34, compromising autophagosome nucleation, while lysosomal dysfunction impairs autophagosome–lysosome fusion and clearance. In parallel, defective selective autophagy of the endoplasmic reticulum (ER-phagy) fails to clear damaged ER, so the unfolded protein response persists and switches from an adaptive to a terminal, pro-apoptotic phase through the PERK–eIF2 α –ATF4–CHOP pathway. The pathways converge at shared nodes—mTOR, PIK3C3/VPS34, reactive oxygen species, calcium transfer at mitochondria-associated ER membranes, and AMP-activated protein kinase—forming one druggable axis rather than two parallel lesions. In experimental sepsis, T cell-specific autophagy deficiency aggravates apoptosis and mortality, whereas mTOR inhibition restores autophagosome–lysosome fusion and rescues CD4⁺ T cells; pharmacological blockade of ER stress is likewise protective. Each node yields a quantifiable pathway activity that could serve as a biomarker for immune-endotype stratification, complementing bedside cues such as lymphocyte counts and checkpoint expression. Building on clinical precedents—recombinant interleukin-7 in the randomized IRIS-7 trial and the Phase 1b study of the anti-PD-1 antibody nivolumab—we appraise strategies that restore the autophagy–ER stress balance, including mTOR inhibitors, ER stress modulators, and autophagy inducers, and outline an agenda of direct flux measurement in patients' T cells, in vivo causal-hierarchy testing, and endotype-stratified trials. The review synthesizes 92 references published between 1999 and 2026; no systematic search or meta-analysis was performed.

Conclusions: Autophagic flux blockade and unresolved endoplasmic reticulum stress are two facets of one stress network driving T cell apoptosis in sepsis. This axis is druggable: biomarker-stratified interventions against it could turn supportive care into precision immunomodulation for sepsis-induced immunosuppression.

1. Introduction

Sepsis is a life-threatening organ dysfunction caused by the host's dysregulated response to infection. It remains the leading cause of death in intensive care units, with an estimated 11 million deaths each year[1]. Early goal-oriented resuscitation therapy and antibiotic treatment have improved the management of the initial high inflammatory stage. However, many patients who survive the cytokine storm still enter a long-term state of immune dysfunction, namely sepsis-induced immunosuppression or immune paralysis, which is currently the main cause of most late deaths, secondary infections and

viral reactivation[2]. This state has been systematically elucidated at both the mechanism and clinical levels and is now regarded as a condition that can be intervened with drugs rather than being irreversible[3]. Hotchkiss et al. shifted the research focus in this field from uncontrolled inflammatory responses to acquired failure of innate and adaptive immunity[4], while recent reviews on mechanisms, biomarkers, and immunotherapy have all focused on the same core message: restoring immune capacity is feasible and has become the core goal of sepsis treatment [5].

T lymphocytes are at the center of this immunosuppression. Autopsy studies on patients who died of sepsis revealed extensive apoptosis of B cells and CD4 + T cells in the spleen and intestinal-related lymphoid tissues, and the degree of lymphocyte loss was associated with the severity and prognosis of the disease [6]. Patients with sepsis consistently exhibit persistent lymphocytopenia and T-cell depletion phenotypes (decreased proliferation capacity, reduced cytokine production, and continuous expression of checkpoint molecules), and these characteristics can predict the risk of nosocomial infection and death [7]. At present, bedside immune surveillance has been able to capture such functional disorders and track their trajectories over time [8]. Innate immune cells also strengthened the above state: myeloid cells acquired immunodeficient phenotypes, and myeloid-derived suppressor cells expanded and inhibited lymphocyte responses[9]. Therefore, clarifying the mechanism of T-cell death in sepsis is a prerequisite for immune regulatory intervention based on the mechanism.

Among numerous candidate mechanisms, two interrelated stress pathways stand out particularly: impaired autophagic flux and the sustained activation of the unfolded protein response (UPR). Autophagy is a lysosomal catabolic process that can maintain cellular homeostasis and protect immune cells during sepsis[10]. T-cell-specific knockout of key autophagy genes can exacerbate apoptosis and mortality in experimental sepsis [11]; Conversely, knocking out the key negative regulatory factor for autophagy initiation - the mechanistic target of rapamycin (mTOR) - can restore autophagosome - lysosomal fusion and reduce the apoptosis of CD4 + T cells in septic mice [12]. Endoplasmic reticulum stress and its downstream unfolded protein response also mediate CD4 + T cell apoptosis in sepsis, and pharmacological inhibition of endoplasmic reticulum stress has a protective effect [13]. Therapeutic strategies targeting these pathways are being actively studied in an effort to reverse sepsis-induced immunosuppression [14]. It is worth noting that the mTOR signaling couples endoplasmic reticulum stress with the apoptotic commitment of CD4 + T cells in sepsis, suggesting that these two pathways form an integrated stress network rather than two isolated cascade reactions[15].

2. T Cell Apoptosis in Sepsis-Induced Immunosuppression

2.1 The biphasic paradigm of sepsis and the immunosuppressive phase

Sepsis has long been regarded as an over-inflammatory syndrome. This view has been replaced by the biphasic model, which holds that a persistent counter-regulatory immunosuppression stage may follow an early high inflammatory response [16]. As supportive treatment can currently help most patients

survive the initial cytokine storm, the majority of sepsis-related deaths occur during this later stage of immune collapse, typically due to secondary infections caused by opportunistic pathogens or low-virulence microbiota[17]. Even at admission, many patients with sepsis present with a mixed state of inflammatory and anti-inflammatory characteristics rather than a simple state of high inflammation. Immunosuppression is a core component that exists in the early stage of the disease rather than a concomitant phenomenon in the late stage[18]. Biological markers of immunosuppression can be detected within several days after the onset of critical illness and are parallel to the evolution trajectory of organ failure[19].

2.2 Clinical and experimental evidence of T cell apoptosis in sepsis

The earliest and most compelling evidence comes from autopsy studies: patients who died of sepsis, shock and multiple organ dysfunction showed significant apoptotic exhaustion of lymphocytes in their lymphoid organs[20]. In human studies, sepsis-induced apoptosis can gradually deplete B cells and CD4 + T cells, while the loss of T cells disproportionately erodes the adaptive immune repertoire [6]. CD4 + T cells in the spleen of mice activate a unique transcriptional program within hours after the onset of sepsis, upregulating pro-apoptotic genes and cell cycle arrest genes[21]. The duration of functional deficiency exceeds the recovery of cell count: Both mouse models and clinical research reports have shown that the CD4 + T cell response remains impaired for a long time even after the lymphocyte count returns to normal[22]. Persistent lymphocytopenia is associated with poor nutritional status and a poor prognosis. Peripheral blood lymphocyte count has been proposed as a simple bedside indicator for evaluating immune paralysis [23]. The expression patterns of exhaustion markers on circulating CD8 + T cells can stratify patients with sepsis and predict their prognosis [24]; Preliminary studies have also confirmed that the expression of PD-1/PD-L1 in each lymphocyte subset has changed, and the levels of soluble checkpoints have increased simultaneously[25].

2.3 Functional consequences: lymphopenia, exhaustion, and secondary infections

Apoptotic loss of T cells can transform into profound functional defects. Both clinical and experimental sepsis can impair CD8⁺ T cell-mediated immune responses, weaken pathogen clearance capabilities and antiviral surveillance functions[26]. The death receptor signaling pathway is involved: Trail-mediated T-cell apoptosis has been considered to be associated with the subsequent immunosuppression[27]. Meanwhile, the surviving lymphocyte bank acquired a depletion phenotype and co-expressed multiple inhibitory receptors. LAG3 and PD-1 follow different expression kinetics and synergistically inhibit T cell function [28]. These pathways are causal rather than accidental because checkpoint blockade can change the outcome: Tim-3 blockade can reduce CD8⁺ T cell apoptosis in septic mice and alleviate the severity of the disease[29]. Bulk and single-cell RNA sequencing of peripheral immune cells has confirmed that the lymphocyte population widely activates the cell death program in sepsis[30].

Therefore, apoptosis-driven lymphocytopenia and checkpoint mediated exhaustion work together to produce clinical immune paralysis (Fig. 1 and Table 1).

Table 1

Representative clinical and experimental evidence of T cell apoptosis and dysfunction in sepsis.

Study type	Model / population	Key finding	Ref.
Autopsy study	Patients dying of sepsis/shock/MODS	Widespread apoptotic lymphocyte death in lymphoid organs	[20]
Human mechanistic study	Septic patients	Progressive, profound depletion of B and CD4 + T cells	[6]
Transcriptional study	Murine splenic CD4 + T cells	Distinct pro-apoptotic transcriptional response within 6 h of sepsis onset	[21]
Longitudinal murine study	Post-sepsis survivors	Long-lasting CD4 + T cell dysfunction despite numerical recovery	[22]
Clinical cohort	Septic patients	CD8 + T cell exhaustion-marker patterns predict outcomes	[24]
Pilot clinical study	Septic patients	Altered PD-1/PD-L1 expression on lymphocyte subsets; elevated soluble checkpoints	[25]
Omics study	Septic patients (bulk + scRNA-seq)	Broad activation of cell-death programs across peripheral immune cells	[30]

The table summarizes representative evidence from the cited studies and is not the result of a systematic literature search. Abbreviations: CD4+, cluster of differentiation 4; CD8+, cluster of differentiation 8; MODS, multiple organ dysfunction syndrome; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; scRNA-seq, single-cell RNA sequencing.

3. Mechanisms of Autophagic Flux Blockade in Immune Cells

3.1 Autophagy as a gatekeeper of T cell survival in sepsis

Autophagy is crucial for T cell homeostasis: it supports the transition of cells from a resting state to an activated state, the quality control of organelles, and survival under metabolic stress conditions[31]. The interpretation of autophagy status requires strict flow cytometry assessment. As emphasized in the international autophagy detection guidelines [32], static LC3-II or p62 measurements are of little significance without lysosomal blockade tests. This pathway is of great significance in sepsis: T-cell-specific Atg7 gene knockout mice exhibit increased apoptosis, suppressed immune response and elevated mortality after cecal ligation and puncture (CLP) [11]. Mitochondrial quality control proteins are interrelated with this mechanism: mitochondrial fusion protein 2 inhibits autophagy, thereby promoting apoptosis of CD4 + T cells in sepsis and linking mitochondrial dynamics with autophagy capacity[33]. This defect is not limited to lymphocytes only. Neutrophils with the CD200Rhigh phenotype in sepsis

have autophagy defects and actively establish systemic immunosuppression[34], while the inhibition of the effector CD4 + T cell response by interleukin-35 involves metabolic and autophagy limitations[35]. Therefore, restoring autophagy has been proposed as a strategy for re-establishing immune homeostasis in critically ill patients [36].

3.2 mTORC1 hyperactivation and suppression of autophagy initiation

mTOR is an evolutionarily conserved serine/threonine kinase that integrates nutritional, energy and growth factor signals to regulate protein synthesis, metabolism and autophagy [37]. In T cells, the participation of T cell receptors (TCRS) activates mTORC1 through CarMA1-dependent and Akt-independent pathways, coupling antigen recognition with metabolic reprogramming [38]. Instantaneous activation of mTORC1 is a necessary condition for effect differentiation; However, continuous excessive activation has harmful effects. In senescent human CD8 + T cells, the p38 MAPK signaling pathway blocks an autophagy pathway independent of mTORC1, which is an example of how stress kinases inhibit the initiation of autophagy in T cells [39]. mTOR activation can also serve as a pathway biomarker in immune-mediated diseases [40]. Most relevant to sepsis is that T-cell-specific mTOR knockout can improve autophagosome-lysosomal fusion and alleviate the apoptosis of CD4 + T cells in CLP mice [12]. Therefore, the excessive activation of mTOR during sepsis drives autophagic flow blockade and lymphocyte death, rather than merely marking these processes. Furthermore, the absence of mTOR reduces pyroptosis of CD4 + T cells by promoting autophagic activity [41], indicating that lifting the inhibition of mTOR can restore autophagic flux and provide protection against more than one mode of cell death.

3.3 The PIK3C3/VPS34–PI3P axis and impaired autophagosome formation

Autophagosome nucleation depends on VPS34 (PIK3C3), a Class III phosphatidylinositol 3-kinase that generates phosphatidylinositol 3-phosphate (PI3P) at the phagocytic vesicles. The activity of VPS34 itself is regulated by post-translational modifications: acetylation can switch the on and off states of its lipid kinase activity, thereby regulating the initiation of classical autophagy[42]. The PI3P library has regionalized characteristics. Stress-induced PI3P generation involves both VPS34-dependent and independent pathways simultaneously. Therefore, the lipid supply required for autophagosome biogenesis is relatively sensitive to upstream disturbances [43]. Downstream of PI3P, the lipidation mechanism of LC3 is finely regulated through the modification of ATG16L1. Zdhhc7-mediated ATG16L1 S-palmitoylation can promote LC3 coupling and autophagosome formation [44]. At present, direct measurement data on the activity of VPS34 in sepsis T cells are still relatively limited. However, the VPS34-PI3P axis is a core link in flux initiation and may be a potential damage site in the overactivated state of mTORC1, as mTORC1 can phosphorylate and inhibit the components of the VPS34-ULK1 initiation complex[37].

3.4 Lysosomal dysfunction and failure of autophagosome clearance

Even if autophagosomes are successfully formed, autophagic flux may still be impaired at the terminal degradation stage. The fusion of autophagosomes and lysosomes depends on lysosomal membrane proteins and transport mechanisms. In septic hearts, the LAMP2-FLOT2 interaction can enhance this fusion process and exert a protective effect [45], suggesting that fusion ability is a regulated and vulnerable key link in sepsis. Inflammatory signals can directly damage the lysosomal compartment: in activated microglia, NLRC5 drives lysosomal dysfunction, disrupts autophagic flux, and continuously maintains an inflammatory state [46]. Therefore, the activation of immune cells can transform lysosomes from homeostatic effectors into victims of inflammation. The autophagy-lysosomal system is also an intervenable target compartment, and its functional failure can reshape cell fate decisions [47]. In sepsis, the initial phase block driven by mTORC1 coexists with lysosomal stress, and autophagic fluxes are squeezed at both ends: on the one hand, the generation of autophagosomes decreases; on the other hand, the clearance efficiency of the already formed autophagosomes is low [12]. These two defects superimpose on each other, making T cells prone to apoptosis.

4. Endoplasmic Reticulum Stress and ER-Phagy Defects

The above-mentioned lysosomal dysfunction also endangers the clearance of endoplasmic reticulum fragments, as their degradation depends on the same autophagosome-lysosomal pathway. When this clearance pathway is blocked, endoplasmic reticulum stress persists without resolution, and the unfolded protein response (UPR) continues. This section will explore the consequences resulting from this.

4.1 The unfolded protein response in septic T cells: PERK–eIF2 α –ATF4–CHOP

The endoplasmic reticulum (ER) is the largest intimal system within cells, coordinating protein folding, lipid synthesis, ion homeostasis and organelle communication. Its continuous renewal is crucial for cellular adaptability[48]. During sepsis, the biosynthetic and secretory demands on immune cells, combined with oxidative and inflammatory stress, exceed the endoplasmic reticulum folding capacity, thereby activating the unfolded protein response (UPR). Endoplasmic reticulum stress is directly involved in the apoptosis of CD4 + T cells in sepsis models: cecal ligation and puncture (CLP) -induced sepsis can activate endoplasmic reticulum stress sensors in CD4 + T cells, and pharmacological inhibition of endoplasmic reticulum stress and its downstream pathways can protect these cells and maintain their functions [49]. The upstream regulation of this response involves the mTOR signaling pathway, which mediates endoplasmic reticulum stress-induced apoptosis of CD4 + T cells in septic mice[13]; Subsequent studies have shown that mTOR partially functions through the generation of reactive oxygen species (ROS) [50]. Dysfunction is not limited to lymphocytes. Dendritic cells from hosts with severe

burns or sepsis exhibit endoplasmic reticulum stress responses, impairs antigen presentation and promotes adaptive immune failure[51], while lipid metabolism reprogramming mediated by SREBF1 leads to immune paralysis of dendritic cells in sepsis[52].

4.2 ER-phagy as ER quality control and consequences of its failure

Selective autophagy of the endoplasmic reticulum (ER-phagy) can eliminate damaged or redundant ER fragments, serving as a first-line quality control mechanism to alleviate endoplasmic reticulum stress. The discovery of FAM134B as an ER-resident autophagy receptor confirmed that the turnover of ER is actively regulated by selective autophagy [48], and the concept and methodological basis of ER-phagy have been thoroughly reviewed [53]. The subtype lineages of ER-phagy and recovER-phagy are still expanding continuously [54]. Mechanistically, FAM134B oligomerization drives ER membrane division, allowing fragments to be encapsulated in autophagosomes and subsequently degraded by lysosomes [55]. A genome-wide screening depicted the complete ER-phagy machine and revealed the unexpected role of mitochondrial metabolism and ER-resident proteins in it[56]. The assembly of the ER-Phagy site is synergistic: UVRAG works in synergy with cargo receptors to recruit autophagy machines to specific ER subdomains [57]. Currently, ER-Phagy probes based on acidic reporting have been able to directly quantify ER autophagic flux in living cells under stress conditions[58]. When the function of ER-Phagy is impaired, misfolded proteins and damaged ER accumulate, UPR activation persists, and the cell signal balance tends towards pro-apoptotic direction. In addition, a broader selective autophagy network also protects T lymphocytes in sepsis: NUFIP1-mediated ribosomal autophagy maintains T cell homeostasis [59].

4.3 From adaptive to terminal UPR: the ER stress–apoptosis switch

UPR has a dual function: the adaptive stage aims to restore protein homeostasis, while the terminal stage performs apoptosis when stress cannot be resolved. The continuous PERK-EIF2 α signaling pathway induces ATF4 and its target gene CHOP, which inhibits anti-apoptotic BCL-2 family members and activates death effector factors, thereby converting endoplasmic reticulum stress into apoptotic signals. In septic CD4 + T cells, this conversion is tightly coupled with upstream metabolic checkpoints. mTOR activity mediates endoplasmic reticulum stress-induced apoptosis. Blocking the mTOR signaling pathway or endoplasmic reticulum stress is sufficient to rescue cells [13]. ROS acts as messengers and amplifiers in this cascade reaction: mTOR-driven ROS production is necessary for endoplasmic reticulum stress-induced apoptosis of CD4 + T cells in sepsis [50], while ROS-induced lipid peroxidation more broadly regulates outcomes at the apoptosis-ferroptosis junction [60]. Mitochondrial dynamics also intersects with the terminal UPR; The division inhibitor MDIV-1 protects CD4 + T cells in sepsis from apoptosis by rebalancing fusion and division[61]. Melatonin elucidates the same principle from a pharmacological perspective, coordinating endoplasmic reticulum stress, autophagy and apoptotic

pathways to promote cell survival [62]. These findings place the adaptive to terminal UPR transition at the decisive checkpoint between endoplasmic reticulum stress and lymphocytopenia in sepsis.

5. Molecular Nodes of Autophagy–ER Stress Crosstalk

Section 3 has confirmed that the autophagic flow of T cells in sepsis is blocked in a continuous phase, ranging from the inhibition of initiation and nucleation to the failure of lysosomal clearance. Section 4 reveals how the persistent endoplasmic reticulum stress maintained by defective endoplasmic reticulum autophagy drives the transition from adaptive to terminal unfolded protein response (UPR) and converts the failure of in situ protein homeostasis that cannot be resolved into apoptotic signals. These two paths do not operate as independent parallel cascades. They converge at shared molecular nodes, forming a single stress network. The following sections will analyze the relevant evidence node by node (Fig. 2).

5.1 mTOR as the central integrator of autophagy and ER stress

The mTOR pathway and endoplasmic reticulum stress response regulate overlapping cellular processes, including apoptosis, autophagy, translation, energy metabolism and inflammatory response [63]. There is two-way communication between these two systems. Endoplasmic reticulum stress can activate or inhibit mTOR signaling depending on specific circumstances, and mTOR activity, in turn, affects the amplitude and duration of unfolded protein response (UPR)[63]. Mechanism studies have shown that mTORC1 interacts with each branch of UPR and coordinates growth signals with protein homeostasis capacity. Continuous mTORC1 activity not only increases the protein folding load but also blocks the autophagy mechanism that could have alleviated this load [64]. This dual effect is particularly important in highly secretory immune cells: in plasma cells, the crosstalk between mTOR and UPR matches the translation output with the endoplasmic reticulum capacity [65]. In sepsis, this integration function turns to a pathological state. mTOR signaling mediates CD4 + T cell apoptosis induced by endoplasmic reticulum stress, thus placing mTOR at a key node where two stress pathways converge [15]. Endoplasmic reticulum stress receptors also interact with inflammasomes and cytokine networks, thus this crosstalk further shapes the immune microenvironment [66].

5.2 Dual roles of PIK3C3/VPS34 in autophagy initiation and ER homeostasis

PIK3C3/VPS34 lipid kinase occupies another key node. In addition to autophagosome nucleation, the PI3P generated by VPS34 also permits the assembly of endoplasmic reticulum autophagy (ER-phagy) sites and the turnover of endoplasmic reticulum subdomains, thereby directly coupling the autophagy machine to endoplasmic reticulum quality control [57]. Endoplasmic reticulum stress-mediated autophagy and endoplasmic reticulum autophagy utilize overlapping but distinct UPR-dependent programs, and UPR itself shapes the choice between the two. Therefore, the VPS34 complex may be differentially deployed depending on the nature and duration of the stress[67]. Post-translational

modification of VPS34 can achieve rapid regulation: The acetylation-dependent switching of its lipid kinase activity enables stress signals to regulate the production of PI3P, and subsequently regulates autophagy initiation and endoplasmic reticulum autophagy [42]. In human diseases, the interaction between endoplasmic reticulum stress and autophagy is regarded as a shared pathogenic module, and the VPS34 axis repeatedly appears as a nodal element [68]. Upstream UPR sensors also affect phosphoinositol metabolism: IRE1 α regulates phosphoinositol signaling lipids and shapes macrophage immune responses, which form a direct communication line between endoplasmic reticulum stress sensors and the lipid landscape dominated by VPS34 [69].

5.3 Auxiliary nodes: Ca²⁺ + signaling, ROS, and AMPK

Multiple auxiliary nodes jointly strengthen this main axis. The first step is calcium treatment at the contact sites of organelles. Mitochondrial-associated endoplasmic reticulum membrane (MAMs) is a signaling platform, and its dysfunction is associated with ischemic and inflammatory pathological processes [70], while protein homeostasis stress can reorganize organelles for contact, thereby triggering calcium-dependent autophagy [71]. MAMs deteriorate with age, which may help explain the phenomenon of excessive immunosuppression in elderly patients with sepsis [72]. ROS constitutes the second hub. Sepsis stimulation induces continuous ROS production, which runs parallel to chronic immune paralysis and lymphopenia [73], and ROS-dependent endoplasmic reticulum stress can trigger autophagy and apoptosis in multiple cell types[74]. System-level analysis of autophagy-apoptosis crosstalk during endoplasmic reticulum stress indicates that ROS and Ca²⁺ are the main information carriers between the two pathways [75]. Finally, the energy receptor AMPK exerts a balancing effect by phosphorylating and inhibiting mTORC1, while promoting autophagy. Moreover, the AMPK-mTORC1 axis has been confirmed to be a regulator of T cell lineage fate and survival[76]. Table 2 summarizes the functions of these nodes and the experimental evidence behind them.

Table 2
Key molecular nodes of autophagy–ER stress crosstalk relevant to septic T cell apoptosis.

Node	Role in autophagy	Role in ER stress	Evidence in sepsis / immune cells	Ref.
mTORC1	Inhibits autophagy initiation (ULK1/VPS34 complexes)	Bidirectional crosstalk with UPR branches	Mediates ER stress–induced CD4 + T cell apoptosis; deletion restores flux and reduces apoptosis	[12], [15]
PIK3C3/VPS34	Generates PI3P for autophagosome nucleation	Licenses ER-phagy site assembly	Activity gated by acetylation; mTOR-dependent suppression links both arms	[42]
FAM134B	ER-phagy receptor driving ER membrane scission	Removes damaged ER, limits UPR signaling	ER turnover failure sustains stress signaling	[55]
PERK–eIF2α–ATF4–CHOP	UPR-induced autophagy gene transcription	Adaptive-to-terminal UPR switch	Active in septic CD4 + T cells; blockade protective	[49]
ROS	Trigger/modulator of autophagy	Amplify ER stress and lipid peroxidation	Prolonged ROS production accompanies septic immunoparalysis	[73]
AMPK	Activates autophagy via mTORC1 inhibition	Attenuates ER stress indirectly	Counter-regulatory energy checkpoint in T cells	[76]
Ca2+ / MAMs	Calcium-dependent autophagy induction	ER–mitochondria Ca2+ transfer fuels apoptosis	Contact-site reorganization under proteostatic stress	[71]

Evidence strength varies by row and matches the text: some rows rest on direct observations in septic T cells, whereas others depend on mechanistic studies or paradigm extrapolation from other cell types or disease contexts. Abbreviations: AMPK, AMP-activated protein kinase; ATF4, activating transcription factor 4; Ca2+, calcium ion; CD4+, cluster of differentiation 4; CHOP, C/EBP homologous protein; eIF2α, eukaryotic initiation factor 2α; ER, endoplasmic reticulum; FAM134B, family with sequence similarity 134 member B; MAMs, mitochondria-associated ER membranes; mTORC1, mechanistic target of rapamycin complex 1; PERK, protein kinase RNA-like ER kinase; PI3P, phosphatidylinositol 3-phosphate; PIK3C3/VPS34, class III phosphoinositide 3-kinase; ROS, reactive oxygen species; ULK1, Unc-51-like autophagy-activating kinase 1; UPR, unfolded protein response.

6. Therapeutic Strategies to Restore the Autophagy–ER Stress Balance

Candidate intervention measures are grouped according to the mechanism nodes they act on. This section first introduces the channel-level drugs acting on this axis (mostly in the preclinical stage), then elaborates on the clinical evidence of lymphocyte-directed immune reconstitution, and finally discusses the deployment strategy of endotype guidance (Fig. 3).

6.1 mTOR inhibitors

In sepsis T cells, inhibiting the mTOR signaling pathway through drug or genetic means is the most direct way to unblock autophagic flux. In the CLP model, T-cell-specific mTOR knockout alleviates CD4 + T cell apoptosis by improving autophagosome-lysosomal fusion, which genetically confirms that mTOR overactivation is a feasible therapeutic target [12]. Rapamycin alleviates organ damage induced by CLP through the inactivation of the NOD-like receptor family pyridine domain-containing protein 3 (NLRP3) inflammasome mediated by autophagy, indicating that drug-induced mTOR inhibition can not only suppress excessive inflammation but also reproduce the above-mentioned protective effect[77]. mTOR deficiency can also protect CD4 + T cells from pyroptosis by enhancing autophagic activity, suggesting that a single intervention measure can increase the threshold of multiple cell death patterns[41]. Given that mTOR activation is a marker of immune dysregulation in multiple diseases, stratifying patients based on mTOR pathway activity may help identify the population most likely to benefit from rapamycin analogue immunomodulatory therapy[40]. However, the pleiotropy of mTOR signaling also needs to be taken seriously: catalytic site inhibitors that simultaneously inhibit mTORC1 and mTORC2 highlight that while deep pathway blocking exerts powerful efficacy, it may also be accompanied by significant toxic reactions [78].

6.2 ER stress modulators

The second strategy directly targets the unfolded protein response (UPR). Existing endoplasmic reticulum (ER) stress modulators include chemical molecular chaperones such as 4-phenylbutyric acid and tauroursodeoxycholic acid, PERK inhibitors and IRE1 α modulators, many of which have shown efficacy in preclinical inflammatory and degenerative disease models[79]. In sepsis, inhibiting endoplasmic reticulum stress and its downstream pathways can protect CD4 + T cells from apoptosis and maintain their function, which confirms the feasibility of unfolded protein response (UPR) as a therapeutic target for immune paralysis[49]. Endoplasmic reticulum stress inhibitors can block the transition from adaptive unfolded protein response (UPR) to end-stage unfolded protein response (UPR) in human disease models [80], and this checkpoint is closely related to sepsis-associated T-cell exhaustion.

6.3 Agents that restore autophagic flux

The third strategy is to restore autophagic flow downstream of the mTOR/PIK3C3 axis or enhance selective autophagic pathways. Carbon monoxide exerts a protective effect in experimental sepsis by enhancing Beclin-1 dependent autophagy[81]; Tasulfonodine induces autophagy and promotes bacterial clearance in multimicrobial sepsis[82]; Semaglutide alleviates myocardial injury in sepsis by inducing

protective autophagy[83]; Melatonin alleviates organ damage in sepsis through SIRT3-mediated autophagy[84]. These four drugs form a consistent pattern in preclinical studies: each drug induces autophagy and exerts a protective effect, but with different mechanisms and targeting different organs. None of the above-mentioned drugs have been directly tested in T cells, but the autophagy-dependent protective effects at the organ level are mechanologically consistent with the restoration of autophagic flow in sepsis T cells and complement the T-cell-specific genetic and pharmacological evidence. Given the coexistence of immunosuppression and maladaptive cell death in sepsis, immune-assisted therapy regimens that regulate the cell death program are increasingly attracting attention as a type of treatment strategy [85].

6.4 Lymphocyte-directed immunotherapy and endotype-guided precision immunomodulation

In addition to the stress pathway itself, immune-based salvage therapies have provided clinical precedents for reversing immune paralysis. In the randomized IRIS-7 trial, interleukin-7 restored lymphocyte counts in patients with septic shock [86], and subsequent systematic reviews supported the use of recombinant human IL-7 for infection-associated lymphopenia [87]. Checkpoint inhibition also has a solid preclinical theoretical basis: PD-L1 blocking improves the survival rate of experimental sepsis by inhibiting lymphocyte apoptosis [88], and a phase 1b trial established the safety of the anti-PD-1 antibody nivolumab in patients with sepsis [89]. In vitro studies have shown that lymphocytes have different response characteristics to nivolumab and IL-7, suggesting that corresponding treatments should be matched based on the mechanism [90]. The end point of this development trajectory is precision immunotherapy guided by immune endotypes, that is, allocating appropriate immunomodulators to each patient at the appropriate time through biomarkers[91]. Candidate biomarkers include lymphocyte count, checkpoint expression, and potential complex metabolic indicators. Under this framework, autophagy-endoplasmic reticulum stress axis modulators will be applied to patients whose endotype is dominated by flux-blocking and terminal UPR signaling, thereby transforming supportive treatment into targeted immune reconstitution[92]. The candidate drugs are summarized in Table 3.

Table 3
Candidate therapeutic agents targeting the autophagy–ER stress axis in sepsis.

Agent	Target / mechanism	Evidence stage	Principal effect	Ref.
Rapamycin	mTORC1 inhibition; restores autophagic flux; NLRP3 inactivation	Preclinical (CLP rodent)	Reduced organ damage; inflammasome suppression	[77]
T cell-specific mTOR deletion	Genetic mTOR ablation	Preclinical (CLP mouse)	Improved autophagosome–lysosome fusion; less CD4 + T cell apoptosis	[12]
Chemical chaperones (4-PBA, TUDCA)	Reduce ER protein-folding load	Preclinical	Interrupt terminal UPR	[79]
ER stress inhibitors (class)	PERK/IRE1 α /ATF6 modulation	Preclinical / translational	Protection of septic CD4 + T cells	[49]
Carbon monoxide	Beclin-1–dependent autophagy induction	Preclinical	Organ protection in sepsis	[81]
Taurolidine	Autophagy induction	Preclinical	Improved bacterial clearance and survival	[82]
Melatonin	SIRT3-mediated autophagy; ER stress dampening	Preclinical	Attenuated septic organ injury	[84]
Semaglutide	Autophagy induction (cardiac)	Preclinical	Reduced septic myocardial injury	[83]
Recombinant human IL-7	T cell expansion / anti-apoptosis	RCT (IRIS-7) + systematic review	Restored lymphocyte counts in septic shock	[86]
Anti-PD-1 (nivolumab)	Checkpoint blockade	Phase 1b (safety established)	Candidate for exhaustion reversal	[89]
Anti-PD-L1	Checkpoint blockade	Preclinical	Improved survival; inhibited lymphocyte apoptosis	[88]

Evidence-stage terminology is used consistently with Fig. 3: Preclinical (CLP), Preclinical/Translational, Phase 1b Clinical, and Randomized Clinical Trial (IRIS-7). Recombinant human IL-7, anti-PD-1, and anti-PD-L1 are vehicles for lymphocyte-directed immune reconstitution rather than direct targets of the autophagy–ER stress axis.

7. Discussion and Conclusions

The evidence collected in this review provides a unified answer to the core issue: autophagic flux blockade and unrelieved endoplasmic reticulum stress in sepsis T cells are two aspects of the same

stress network, rather than parallel and independent lesions. At the top of this network, excessive activation of mTOR simultaneously inhibits autophagy initiation and amplifies endoplasmic reticulum stress-driven apoptotic signals. PIK3C3/VPS34 lipid kinase couples autophagosome nucleation with endoplasmic reticulum quality control by allowing endoplasmic reticulum autophagy (ER-phagy) on the damaged endoplasmic reticulum subdomain. The Ca^{2+} transfer at MAMs, continuous ROS generation, and AMPK energy checkpoints jointly regulate the gain of this axis. These auxiliary nodes may explain the differences in the depth and duration of immune paralysis among individuals. When protein homeostasis cannot be restored, the end-stage UPR switch prompts T cells to undergo apoptosis and consolidates the immunosuppression induced by sepsis. Therefore, this network is an interventionable space rather than a passive reading of cell damage.

This model has translational medical significance because each node provides measurable readout indicators or clear drug targets. The mTORC1 signaling pathway, autophagy flux and unfolded protein response amplitude are all quantifiable pathway activities and can be used as biomarkers for intramolecular classification in patients with sepsis. mTOR inhibitors, endoplasmic reticulum stress regulators and autophagy inducers respectively act on different nodes of this network, making it a candidate for drug relocalization. The rational combination of these drugs with lymphocyte-directed immunotherapy (such as IL-7 or checkpoint blockade) may achieve durable immune reconstitution. Readout indicators based on this signal axis will help identify patient groups whose immunosuppression is driven by this network and who are most likely to benefit from these treatment regimens.

The conclusion of this comprehensive analysis is limited by the evidence on which it is based. The direct evidence mainly comes from CD4 + T cells and rodent CLP models, so its generalization to human sepsis still belongs to a speculative nature. In T cells of patients with sepsis, autophagic flux and endoplasmic reticulum autophagy have not been directly quantitatively analyzed, and data on the activity of the PIK3C3/VPS34 complex in sepsis T cells are relatively scarce. Most institutional conclusions are derived from genetic and pharmacological intervention studies. In a complete organism, the causal hierarchical relationships among the cross-dialogue nodes of various signaling pathways remain unclear. At present, there are no clinical trials directly testing whether drugs targeting this signaling axis have measurable clinical benefits in sepsis. The existing research results of IL-7 and anti-PD-1 only support immune reconstitution as a therapeutic strategy and have not directly verified this signaling axis.

These boundaries define a specific research agenda rather than openly calling for more research. The primary task is to directly measure the autophagic flux and endoplasmic reticulum autophagy in T cells of patients with sepsis, and distinguish the abundance of autophagic flux from that of static markers. Secondly, it is necessary to establish the causal hierarchical relationship among each node in vivo through conditional genetics or timed pharmacological inhibition methods. Thirdly, design trials based on biomarker stratification to verify whether restoring autophagy-endoplasmic reticulum stress balance can improve clinical outcomes. The research progress on these three issues is expected to transform the interpretation of the molecular mechanism of T-cell death in sepsis into precise immunomodulatory strategies at the bedside.

Abbreviations

4-phenylbutyrate (4-PBA); AMP-activated protein kinase (AMPK); activating transcription factor 4 (ATF4); autophagy-related 16-like 1 (ATG16L1); B-cell lymphoma 2 (BCL-2); calcium ion (Ca²⁺); C/EBP homologous protein (CHOP); cecal ligation and puncture (CLP); cluster of differentiation 4 (CD4+); cluster of differentiation 8 (CD8+); endoplasmic reticulum (ER); eukaryotic initiation factor 2 α (eIF2 α); family with sequence similarity 134 member B (FAM134B); flotillin-2 (FLOT2); inositol-requiring enzyme 1 α (IRE1 α); intensive care unit (ICU); interleukin-7 (IL-7); lysosomal-associated membrane protein 2 (LAMP2); lymphocyte activation gene 3 (LAG3); mechanistic target of rapamycin (mTOR); mechanistic target of rapamycin complex 1 (mTORC1); microtubule-associated protein 1 light chain 3 (LC3); mitochondria-associated ER membranes (MAMs); multiple organ dysfunction syndrome (MODS); NOD-like receptor family pyrin domain-containing protein 3 (NLRP3); nuclear FMR1-interacting protein 1 (NUFIP1); phosphatidylinositol 3-phosphate (PI3P); class III phosphoinositide 3-kinase (PIK3C3/VPS34); programmed cell death protein 1 (PD-1); programmed death-ligand 1 (PD-L1); protein kinase RNA-like ER kinase (PERK); reactive oxygen species (ROS); recombinant human IL-7 (rhIL-7); single-cell RNA sequencing (scRNA-seq); sirtuin 3 (SIRT3); sterol regulatory element-binding transcription factor 1 (SREBF1); tauroursodeoxycholic acid (TUDCA); T-cell immunoglobulin and mucin domain-containing protein 3 (Tim-3); TNF-related apoptosis-inducing ligand (TRAIL); TNF-related apoptosis-inducing ligand receptor (TRAIL-R); Unc-51-like autophagy-activating kinase 1 (ULK1); unfolded protein response (UPR); UV radiation resistance-associated gene (UVRAG)

Declarations

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Author Contributions:

Conceptualization, Wei Yin and Sun Liu; writing—original draft preparation, [Wei Jiang]; writing—review and editing, [Junjie Yu and Chen Chen]; visualization, [Lihui Luo]; supervision, [Shouhui Xiong]; funding acquisition, [Wei Yin and Xianhua Zeng]. All authors have read and agreed to the published version of the manuscript.

Funding:

This research was funded by [Changde City Science and Technology Innovation Project]. The predictive value of a new biological indicator, creatinine-to-albumin ratio (CAR), for patients with septic shock and septic cardiomyopathy], grant number [2024ZD273].

Conflicts of Interest:

The authors declare no conflicts of interest.

Data Availability Statement:

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments:

During the preparation of this manuscript, the authors used Figdraw for Figure.

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Figures

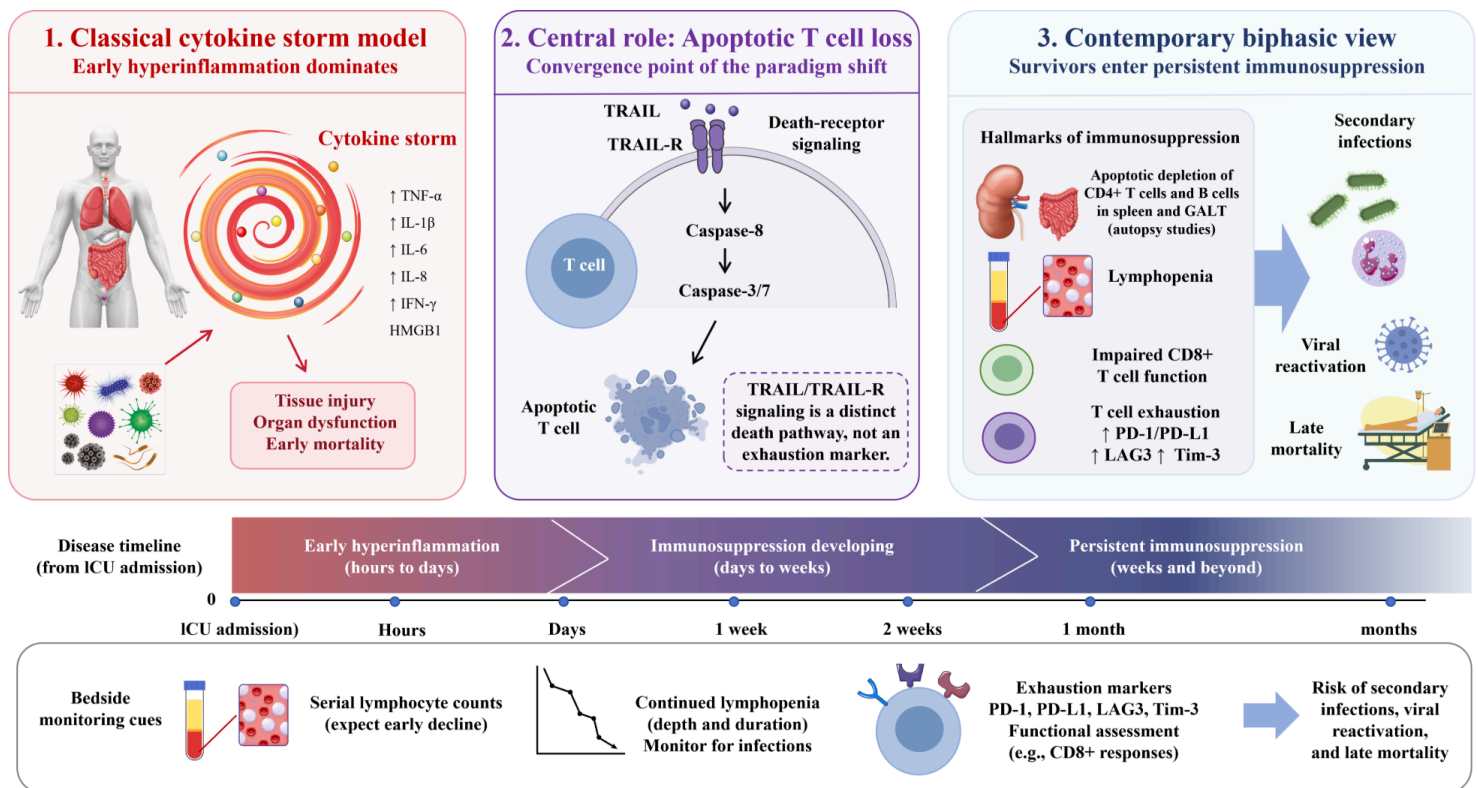


Figure 1

The paradigm shift in sepsis immunology and the central role of T cell apoptosis in sepsis-induced immunosuppression. Panel 1 (left): the classical cytokine storm model, in which early hyperinflammation dominates the clinical course; elevated TNF- α , IL-1 β , IL-6, IL-8, IFN- γ , and HMGB1 drive tissue injury, organ dysfunction, and early mortality. Panel 2 (center): apoptotic T cell loss as the convergence point of the paradigm shift; death-receptor signaling through TRAIL/TRAIL-R activates caspase-8 and caspase-3/7, culminating in T cell apoptosis. TRAIL/TRAIL-R signaling is a distinct death pathway rather than an exhaustion marker. Panel 3 (right): the contemporary biphasic view, in which survivors of the initial phase enter persistent immunosuppression; hallmarks include apoptotic depletion of CD4+ T cells and B cells in the spleen and gut-associated lymphoid tissue (GALT, documented in autopsy studies), lymphopenia, impaired CD8+ T cell function, and a T cell exhaustion phenotype with increased PD-1/PD-L1, LAG3, and Tim-3. These changes promote secondary infections, viral reactivation, and late mortality. Bottom: disease timeline from ICU admission, spanning early hyperinflammation (hours to days), developing immunosuppression (days to weeks), and persistent immunosuppression (weeks and beyond), with bedside monitoring cues (serial lymphocyte counts, depth and duration of lymphopenia, exhaustion-marker expression, and functional assessment such as CD8+ responses) linked to the risk of secondary infections, viral reactivation, and late mortality. Abbreviations: GALT, gut-associated lymphoid tissue; HMGB1, high-mobility group box 1; ICU, intensive care unit; IFN- γ , interferon- γ ; IL, interleukin; LAG3, lymphocyte activation gene 3; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Tim-3, T-cell immunoglobulin and mucin domain-containing protein 3; TNF- α , tumor necrosis factor- α ; TRAIL, TNF-related apoptosis-inducing ligand; TRAIL-R, TRAIL receptor.

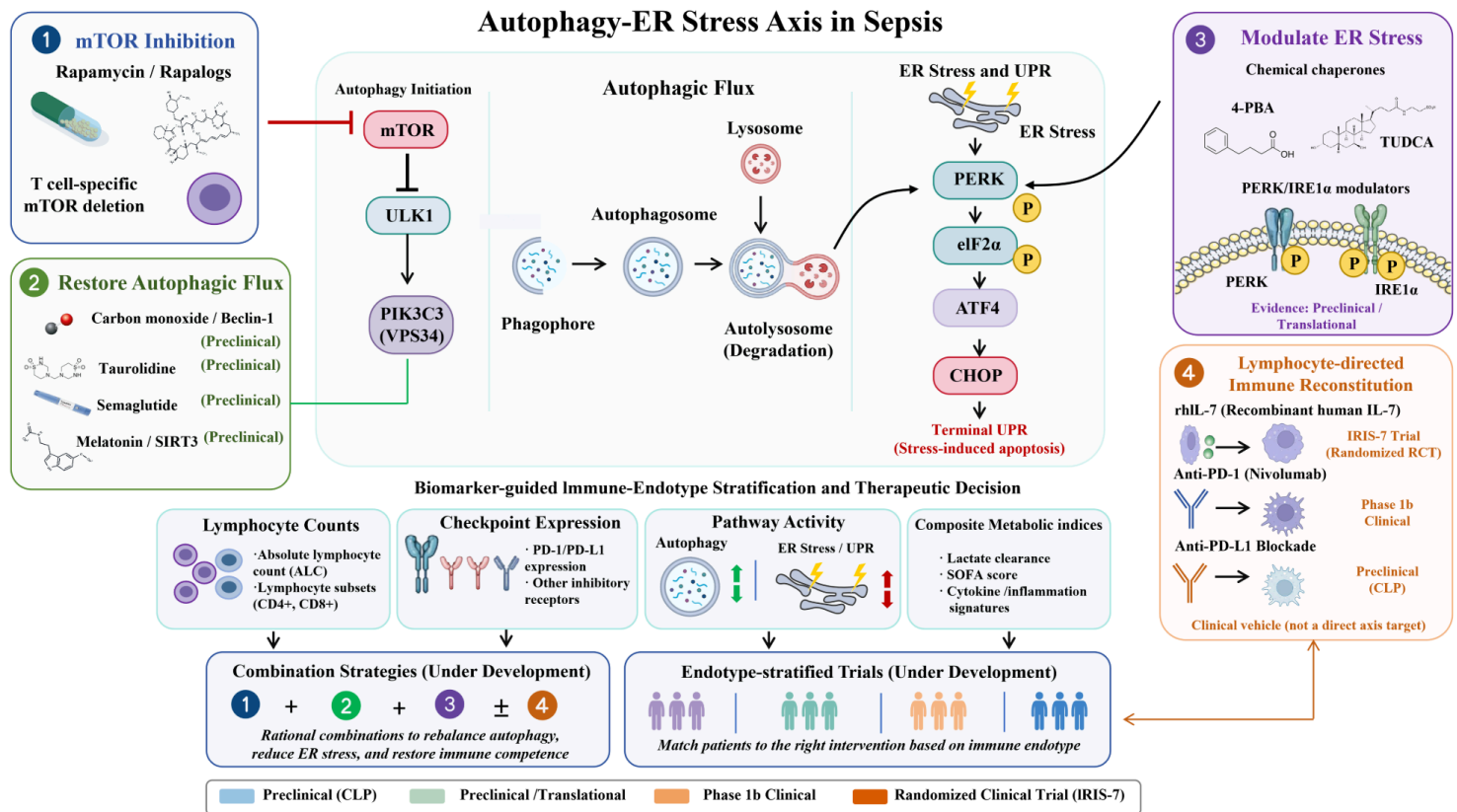


Figure 2

The mTORC1–PIK3C3/VPS34–autophagic flux–ER stress axis in septic T cells. The schematic is organized into an input band (top), a central mechanism band, and an output band (bottom). Input: the septic microenvironment, nutrient signals (amino acids, glucose), energy status (high ATP/low AMP), and growth factor, cytokine, and T cell receptor (TCR) signals converge on mechanistic target of rapamycin complex 1 (mTORC1); AMP-activated protein kinase (AMPK) counter-regulates mTORC1. (A) Autophagic flux blockade: mTORC1 suppresses the ULK1 initiation complex and the class III phosphoinositide 3-kinase PIK3C3/VPS34; reduced phosphatidylinositol 3-phosphate (PI3P) production, defective LC3 lipidation, and impaired ATG16L1 function compromise phagophore initiation and autophagosome nucleation, whereas lysosomal dysfunction and defective LAMP2/FLOT2-mediated fusion impair fusion and clearance—flux is therefore blocked at both generation and degradation. (B) Endoplasmic reticulum (ER) stress: increased protein-folding load sustains the unfolded protein response (UPR) through the PERK–eIF2α–ATF4–CHOP pathway, and FAM134B/UVRAG-dependent ER-phagy fails to clear damaged ER. (C) Crosstalk integration nodes: mTORC1, AMPK, and PIK3C3/VPS34 integrate the network, amplified by reactive oxygen species (ROS) and Ca²⁺ transfer at mitochondria-associated ER membranes (MAMs). Output: the adaptive-to-terminal UPR switch culminates in CD4⁺ T cell apoptosis and sepsis-induced immunosuppression. Solid arrows denote established or mechanistically supported relationships; dashed arrows denote indirect or paradigm-extrapolated relationships; red bar-ended lines denote inhibition. Labels A–C mark functional modules within the figure, not independent subpanels. Abbreviations: AMPK, AMP-activated protein kinase; ATF4, activating transcription factor 4; ATG16L1, autophagy-related 16-like 1; Ca²⁺, calcium ion; CHOP, C/EBP

homologous protein; eIF2α, eukaryotic initiation factor 2α; ER, endoplasmic reticulum; FAM134B, family with sequence similarity 134 member B; FLOT2, flotillin-2; LAMP2, lysosome-associated membrane protein 2; LC3, microtubule-associated protein 1 light chain 3; MAMs, mitochondria-associated ER membranes; mTORC1, mechanistic target of rapamycin complex 1; PERK, protein kinase RNA-like ER kinase; PI3P, phosphatidylinositol 3-phosphate; PIK3C3/VPS34, class III phosphoinositide 3-kinase; ROS, reactive oxygen species; TCR, T cell receptor; ULK1, Unc-51-like autophagy-activating kinase 1; UPR, unfolded protein response; UVRAG, UV radiation resistance-associated gene.

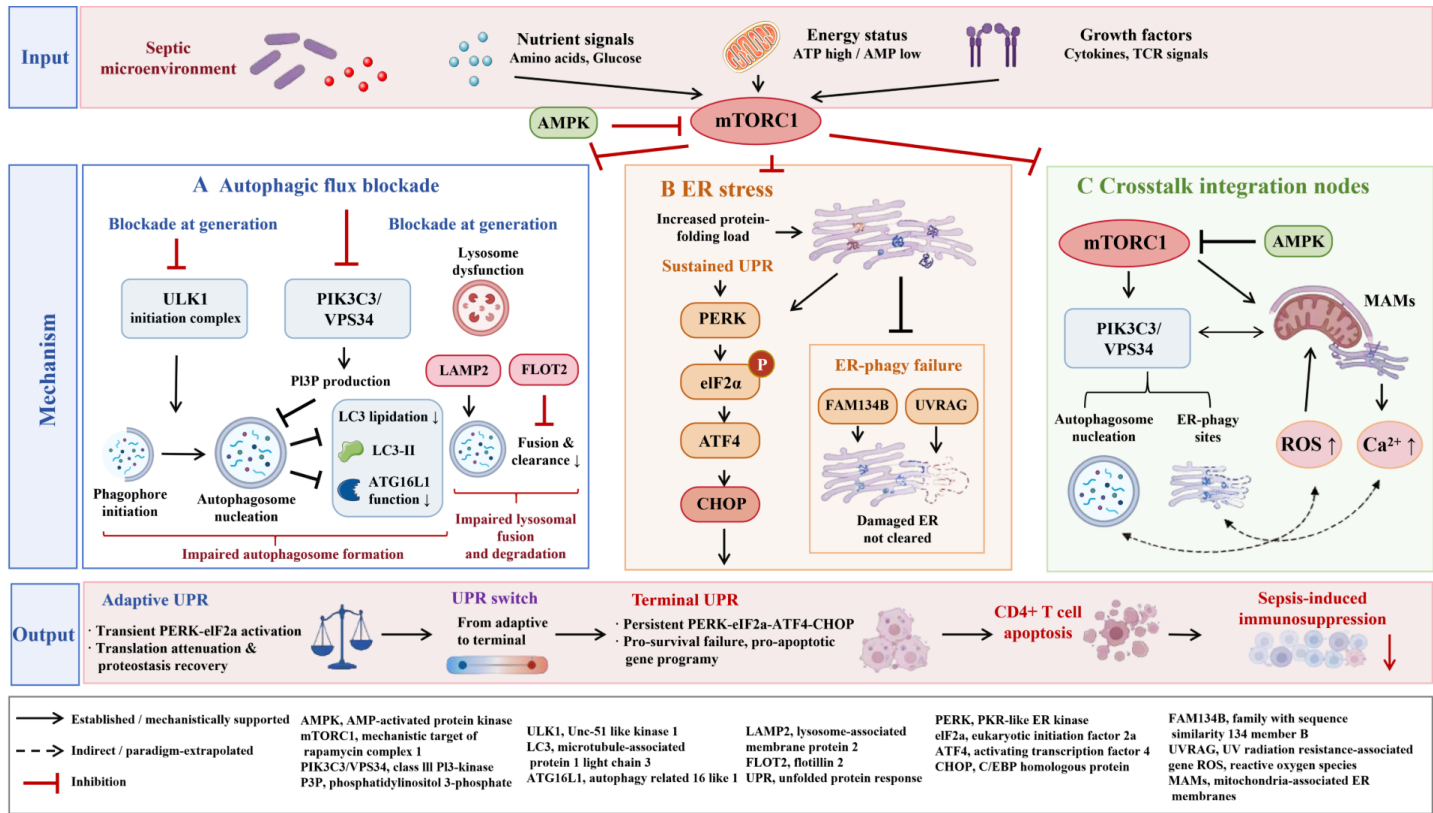


Figure 3

Therapeutic targeting of the autophagy–ER stress axis in sepsis. Candidate interventions are mapped onto the mechanistic axis that couples autophagy initiation (mTOR–ULK1–PIK3C3/VPS34) and autophagic flux (phagophore → autophagosome → autolysosome formation and lysosomal degradation) with endoplasmic reticulum (ER) stress progressing through PERK–eIF2α–ATF4–CHOP to the terminal unfolded protein response (UPR) and stress-induced apoptosis. Four intervention groups are shown. Group 1, mTOR inhibition (rapamycin/rapalogs; T cell–specific mTOR deletion), is supported by preclinical cecal ligation and puncture (CLP) models. Group 2 restores autophagic flux with carbon monoxide/Beclin-1, tauroclidine, semaglutide, and melatonin/SIRT3 (all preclinical). Group 3 modulates ER stress with the chemical chaperones 4-phenylbutyrate (4-PBA) and tauroursodeoxycholic acid (TUDCA) or with PERK/IRE1α modulators (preclinical/translational). Group 4, lymphocyte-directed immune reconstitution, is a clinical vehicle rather than a direct axis target: recombinant human IL-7 (rhIL-7; the randomized IRIS-7 trial), anti-PD-1 (nivolumab; Phase 1b safety study), and anti-PD-L1 blockade (preclinical, CLP). The lower decision layer depicts biomarker-guided immune-endotype stratification

(lymphocyte counts, checkpoint expression, autophagy and ER stress/UPR pathway activity, and composite metabolic indices) feeding into combination strategies (Groups 1 + 2 + 3 ± 4) and endotype-stratified trials, both under development. Box colors denote the evidence stage of each strategy: blue, preclinical (CLP); green, preclinical/translational; light orange, Phase 1b clinical; dark orange, randomized clinical trial (IRIS-7). Abbreviations: CLP, cecal ligation and puncture; ER, endoplasmic reticulum; IL-7, interleukin-7; IRE1 α , inositol-requiring enzyme 1 α ; mTOR, mechanistic target of rapamycin; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PERK, protein kinase RNA-like ER kinase; PIK3C3/VPS34, class III phosphoinositide 3-kinase; SIRT3, sirtuin 3; UPR, unfolded protein response.