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Regulated cell death in sepsis-associated liver injury: molecular mechanisms and therapeutic implications

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Sepsis-associated liver injury (SALI) is a critical determinant of sepsis prognosis, characterized by extensive hepatocellular death and dysregulated immune responses. Emerging evidence highlights the pivotal role of regulated cell death (RCD) – including apoptosis, necroptosis, pyroptosis, and ferroptosis – in driving hepatic dysfunction and systemic inflammation. These cell death modalities, once considered distinct, are now recognized as components of an interconnected network that integrates inflammatory, metabolic, and oxidative signals within the liver's unique immunometabolic microenvironment. This review systematically summarizes the molecular mechanisms of major RCD pathways implicated in SALI, and elucidates their crosstalk and convergence through shared mediators such as caspase-8, the NLRP3 inflammasome, lipid peroxidation, and liver-specific metabolic regulators including bile acid signaling. We further discuss key signaling cascades including PI3K/Akt, Nrf2, and NF- κ B that orchestrate RCD execution and inflammatory amplification in SALI. By integrating mechanistic insights with emerging translational perspectives, this review highlights RCD as a unifying framework for understanding liver injury and identifying therapeutic entry points to restore hepatic and systemic homeostasis during sepsis.

KEYWORDS

bile acid metabolism, ferroptosis, immune dysregulation, lipid peroxidation, pyroptosis, regulated cell death, sepsis-associated liver injury

1 Introduction

Sepsis, defined as a dysregulated host response to infection causing life-threatening organ dysfunction, remains a major global public health burden (1). In 2017, an estimated 48.9 million sepsis cases and 11 million associated deaths occurred worldwide, accounting for nearly 20% of global mortality (2). Among the affected organs, the liver serves as both a key target and an active participant in sepsis pathophysiology. Sepsis-associated liver injury (SALI) occurs in approximately one-third of patients and carries a mortality rate between 54%–68% (3, 4). Hepatic dysfunction has thus been recognized as an independent predictor of poor prognosis in sepsis.

As a central metabolic and immunological hub, the liver plays vital roles in pathogen clearance, cytokine production, and acute-phase protein synthesis. However, this centrality

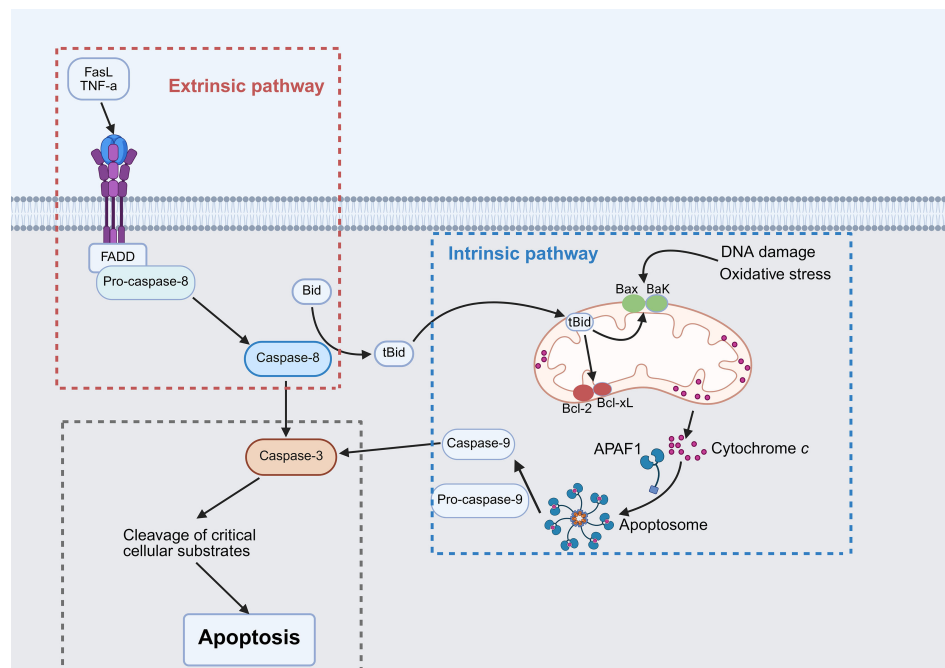


FIGURE 1

Schematic representation of apoptotic pathways. The intrinsic pathway is initiated by intracellular stress signals, while the extrinsic pathway is triggered by extracellular death ligands. Both pathways converge on activated caspase-3, which cleaves cellular substrates to induce apoptosis.

also renders it highly susceptible to damage under excessive systemic inflammation and oxidative stress (5, 6). Recently, regulated cell death (RCD) has emerged as a critical contributor to hepatocellular injury during sepsis. Distinct forms of RCD—including apoptosis, necroptosis, pyroptosis, and ferroptosis—cooperate and intersect to drive hepatocyte loss and immune dysregulation (7–9). Understanding their mechanisms and interconnections is essential for developing targeted interventions. This review summarizes the current knowledge of these major RCD pathways in SALI, highlights their molecular crosstalk, and discusses key intracellular signaling cascades that regulate these processes.

2 Major forms of RCD in SALI

2.1 Apoptosis: classical caspase-mediated hepatocyte death

Apoptosis is a caspase-dependent, non-inflammatory form of RCD that eliminates damaged or infected cells to maintain homeostasis (10). Morphologically, apoptotic cells exhibit membrane blebbing, chromatin condensation, and formation of apoptotic bodies. Apoptosis proceeds through two canonical pathways: intrinsic and extrinsic (Figure 1). The intrinsic (mitochondrial) pathway is regulated by Bcl-2 family proteins that control mitochondrial membrane permeability (11). Activation of Bax/Bak promotes cytochrome *c* (Cyt-*c*) release, triggering apoptosome formation and sequential activation of caspase-9 and caspase-3 (12). The extrinsic (death receptor)

pathway is initiated when extracellular ligands such as tumor necrosis factor (TNF) or Fas ligand (FasL) bind their respective receptors, leading to Fas-associated protein with a death domain (FADD) recruitment and caspase-8 activation, which directly cleaves caspase-3 (13).

In SALI, lipopolysaccharide (LPS) and inflammatory cytokines promote hepatocyte apoptosis through caspase-3 activation and dysregulation of Bax/Bcl-2 expression (14, 15). Bid serves as a molecular bridge between intrinsic and extrinsic pathways; its deletion attenuates hepatocyte apoptosis and improves survival in septic models (16). Upstream regulators, including endoplasmic reticulum stress (17), P2Y2 purinergic signaling (18), and microRNAs (e.g., miR-30a, miR-103a-3p) (19, 20), further fine-tune apoptotic cascades. Therapeutically, anti-apoptotic agents including menthol (21), obeticholic acid (22), and fibroblast growth factor 19 (FGF19) (23) confer hepatoprotection by suppressing caspase activation and oxidative stress, with menthol additionally improving survival, and obeticholic acid and FGF19 restoring bile acid homeostasis in experimental sepsis models. Collectively, apoptosis represents a central mechanism of hepatocyte loss in SALI, and modulation of its key regulators offers promising therapeutic potential.

2.2 Necroptosis: programmed necrosis amplifying inflammation

Necroptosis is a caspase-independent, regulated necrotic process characterized by cell swelling, plasma membrane rupture and release of damage-associated molecular patterns (DAMPs) (24). It is primarily governed by receptor-interacting protein kinase 1 (RIPK1)–RIPK3–mixed lineage kinase domain-like protein (MLKL)

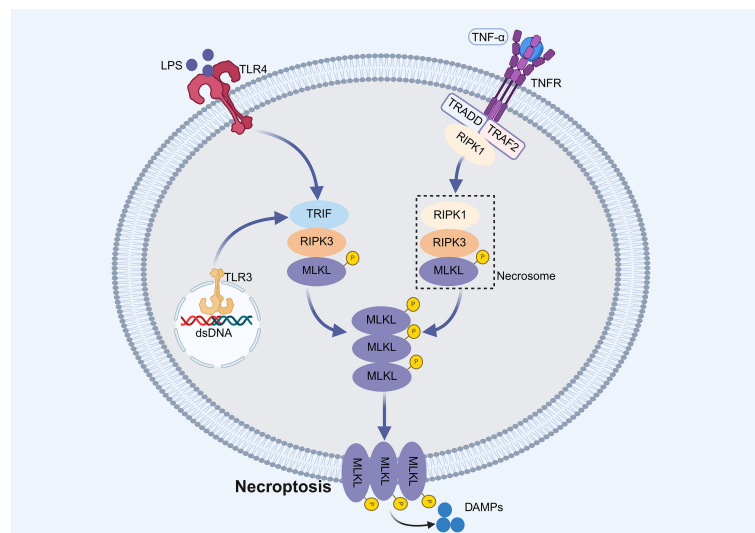


FIGURE 2

Schematic representation of necroptosis pathways. Activation of death receptors or Toll-like receptors recruits RHIM domain-containing proteins to engage RIPK3. Activated RIPK3 phosphorylates MLKL, which oligomerizes and translocates to the plasma membrane, resulting in plasma membrane rupture and necroptotic cell death.

signaling axis (25). Upon activation of death receptors (e.g., TNFR) or certain Toll-like receptors (TLRs), RIPK1 recruits RIPK3 through RIP homotypic interaction motif (RHIM)-mediated interactions; RIPK3 then phosphorylates MLKL, which oligomerizes and disrupts the plasma membrane (26, 27) (Figure 2).

Necroptosis is markedly activated in septic livers, evidenced by elevated RIPK1, RIPK3, and p-MLKL expression (28–30). While moderate necroptosis may contribute to antimicrobial defense (31), excessive activation amplifies inflammation and tissue injury (30). Intriguingly, pharmacological inhibition of necroptosis (e.g., necrostatin-1) has yielded inconsistent outcomes—attenuating necroptosis but sometimes worsening survival—highlighting its context-dependent dual role in SALI (32). Thus, selective modulation rather than complete suppression may be necessary for therapeutic efficacy.

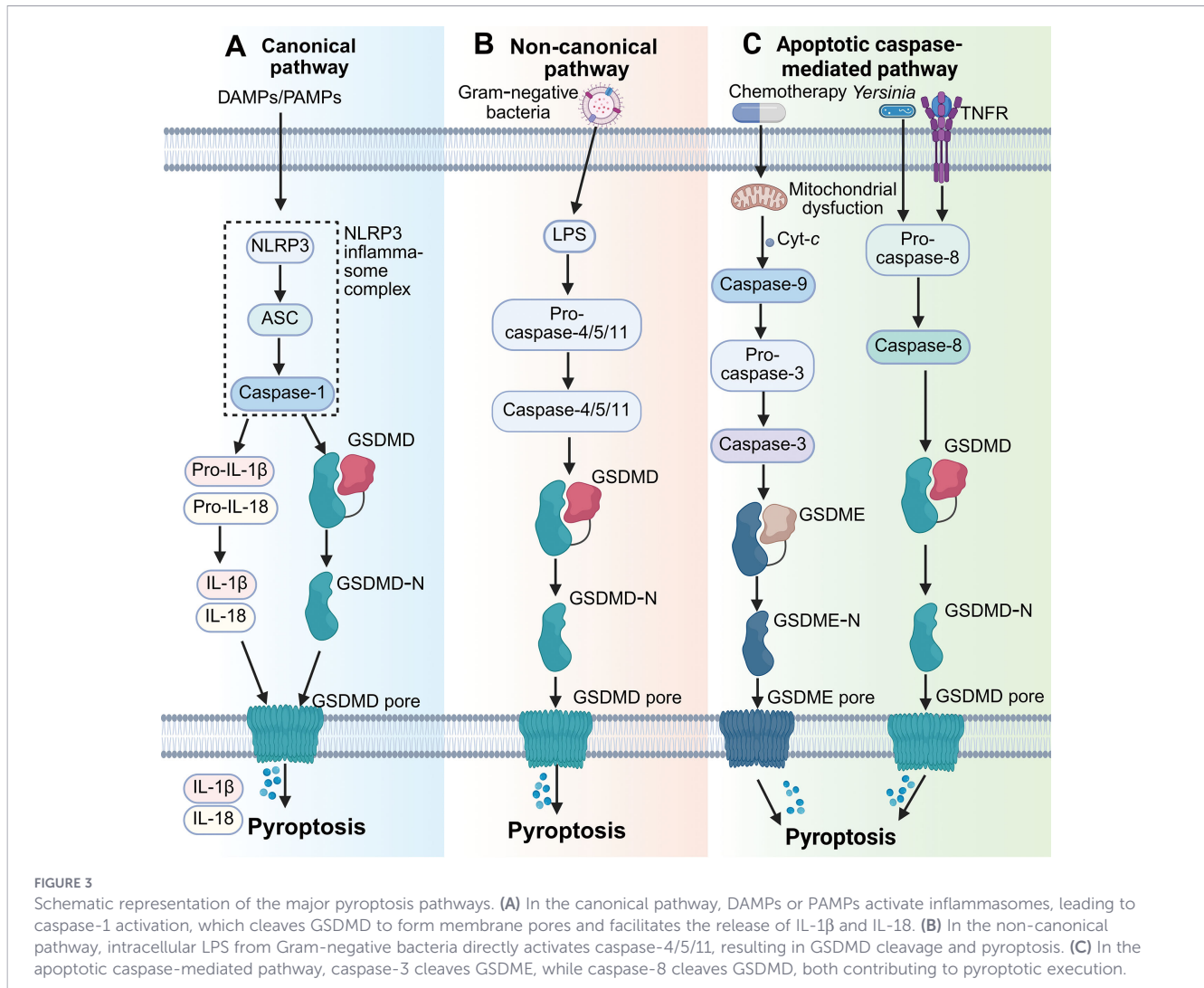
2.3 Pyroptosis: inflammasome-driven inflammatory cell death

Pyroptosis is an inflammatory form of RCD mediated by gasdermin family proteins and inflammatory caspases (33). Pyroptosis can be initiated via three major routes: the canonical inflammasome pathway, the non-canonical inflammasome pathway, and the caspase-3/gasdermin E (GSDME)-mediated pathway. In the canonical pathway, activation of pattern recognition receptors (PRRs), such as nucleotide-binding domain and leucine-rich repeat related (NLR) family pyrin domain containing 3 (NLRP3), recruits apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) and caspase-1 to assemble the inflammasome complex. Activated caspase-1 then cleaves gasdermin D (GSDMD) and facilitates the release of IL-1 β and IL-18 (34, 35). The non-canonical pathway is triggered by cytosolic LPS directly activating caspase-4/5/11,

leading to GSDMD cleavage and pyroptosis independently of NLRP3 (36). Additionally, pyroptosis can be engaged through a caspase-3/GSDME-dependent pathway, in which apoptotic caspase-3 cleaves GSDME, thereby converting apoptosis into secondary pyroptotic cell death (37). Under certain infectious conditions, caspase-8 can also induce pyroptosis via GSDMD processing, such as during *Yersinia* infection (38) (Figure 3).

In SALI, excessive pyroptosis amplifies hepatic inflammation. LPS and DAMPs induce caspase-11–GSDMD–dependent hepatocyte pyroptosis, while GSDME-mediated pyroptosis further aggravates damage (9, 39). Inflammasome activation in Kupffer and hepatocytes disrupts immune tolerance and promotes cytokine storm and hepatic necroinflammation (40, 41). Therapeutic agents such as maresin 1, samotolisib, and irisin have shown efficacy in inhibiting NLRP3 inflammasome or caspase-11–mediated pyroptosis (42–44). Hence, controlled modulation of pyroptosis represents a promising avenue to mitigate inflammatory liver injury and restore immune balance during SALI.

Importantly, beyond serving as an executioner of inflammatory cell death, pyroptosis critically shapes immune homeostasis during sepsis (45). Excessive inflammasome-driven pyroptosis results in robust release of IL-1 β and IL-18, enhancing pathological leukocyte recruitment, and aggravating tissue inflammation. In parallel, sustained pyroptotic death of innate immune cells, including macrophages and dendritic cells, contributes to immune cell depletion and subsequent immunosuppression (46). Therefore, therapeutic modulation of pyroptosis has the potential to rebalance host immunity during sepsis by simultaneously restraining hyperinflammation in the early phase and preserving immune cell competence in later stages, thereby limiting immunopathology while preventing immune paralysis (47). This dual role positions pyroptosis as a critical regulatory node linking inflammatory amplification to immune dysregulation in SALI.



2.4 Ferroptosis: iron-dependent lipid peroxidation–induced hepatocyte injury

Ferroptosis, first described by Dixon et al. in 2012, is driven by iron-dependent lipid peroxidation resulting from redox imbalance (48). It features mitochondrial shrinkage, cristae loss, and outer membrane rupture (49). Mechanistically, excess Fe²⁺ catalyzes the Fenton reaction, generating reactive oxygen species (ROS) that oxidize polyunsaturated fatty acids (PUFAs)-containing phospholipids (50, 51). Two antioxidant systems counteract this process: the cystine/glutamate antiporter (system X_c⁻)–glutathione (GSH)–glutathione peroxidase 4 (GPX4) axis, converting toxic phospholipid hydroperoxides to non-toxic forms (52); the ferroptosis suppressor protein 1 (FSP1)–coenzyme Q₁₀ (CoQ₁₀) and vitamin K reduction systems, which scavenge free radicals (53, 54) (Figure 4).

Clinically, these molecular features of ferroptosis are highly relevant to sepsis pathophysiology. Red blood cell lysis and hemolysis are common features of severe sepsis and septic shock, resulting in the release of free heme and iron into the circulation (55). Elevated plasma free heme levels have been consistently associated with disease severity, organ dysfunction, and increased mortality in septic patients (56, 57). Once released, heme is rapidly

taken up by the liver, where its degradation and the ensuing iron overload promote oxidative stress and lipid peroxidation. This heme-driven iron excess provides a direct pathological link between systemic hemolysis during sepsis and ferroptosis-prone hepatocyte injury, thereby connecting clinical sepsis phenotypes with iron-dependent lipid peroxidation and RCD in SALI (58).

In SALI, inhibition of ferroptosis mitigates hepatic dysfunction and improves survival. Key regulators include G protein-coupled receptor 116 (GPR116), which promotes ferroptosis by suppressing GPX4 (59), and Yes-associated protein 1 (YAP1), which prevents ferritinophagy (60). Protective factors such as milk fat globule-EGF factor 8 (MFG-E8) and irisin enhance GPX4 expression and antioxidant defenses (61, 62). Other mediators, including pentraxin-3, neuregulin 4, and maresin 1, also protect against SALI by modulating ferroptosis-related signaling pathways such as the nuclear factor erythroid 2-related factor 2 (Nrf2)/solute carrier family 7 member 11 (SLC7A11)/GPX4 axis (63–65). Pharmacological inhibition, for instance by quercetin, suppresses ferritinophagy and reduces intracellular iron overload, thereby mitigating LPS-induced injury (66). Collectively, ferroptosis represents a critical intersection between oxidative stress, lipid metabolism, and hepatocyte death in sepsis.

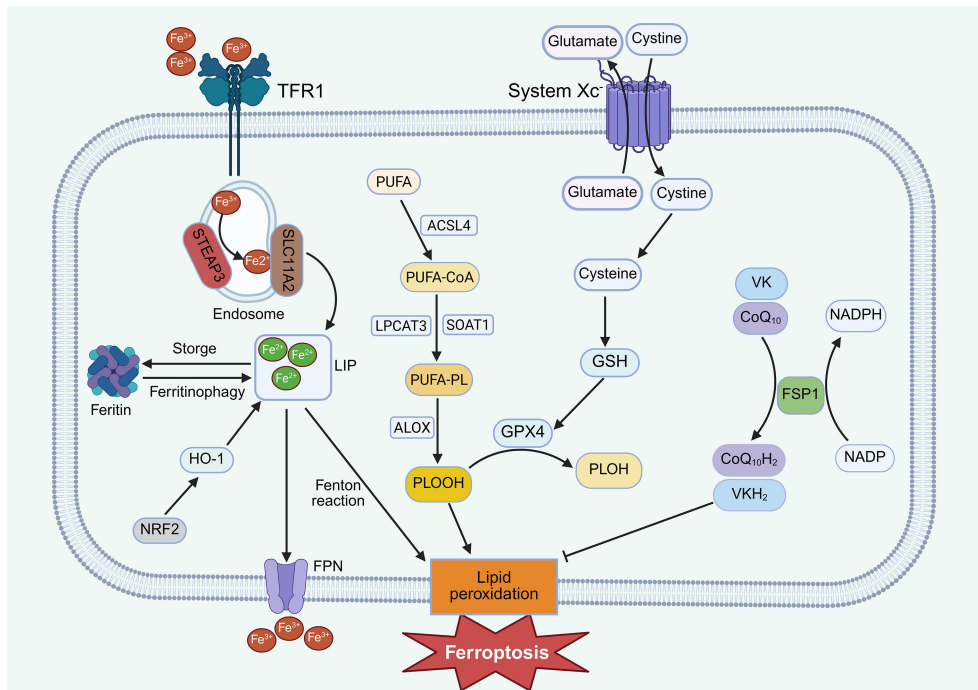


FIGURE 4 Schematic representation of ferroptosis pathways. Extracellular Fe³⁺ enters cells via TFR1-mediated endocytosis and is reduced to Fe²⁺ in the labile iron pool (LIP). Excess Fe²⁺ catalyzes Fenton reactions, producing ROS that induce oxidative membrane damage. The system Xc⁻ transporter imports cystine to sustain GSH synthesis, while GPX4 utilizes GSH to convert PLOOHs to non-toxic PLOHs, thereby suppressing ferroptosis. In addition, FSP1-mediated regeneration of reduced CoQ₁₀H₂ and VKH₂ provides an independent antioxidant system that scavenges lipid radicals and suppresses ferroptosis.

2.5 Comparative features of major RCD modalities in SALI

Although apoptosis, pyroptosis, necroptosis, and ferroptosis represent distinct forms of RCD, they contribute to SALI through partially overlapping yet functionally divergent mechanisms. Apoptosis predominates in hepatocytes during early phases of sepsis and is generally considered less immunogenic, serving as a homeostatic mechanism to eliminate damaged cells. In contrast, pyroptosis and necroptosis are highly inflammatory and occur predominantly in innate immune cells such as Kupffer cells and infiltrating macrophages, amplifying cytokine release and hepatic immune dysregulation. Ferroptosis, driven by iron-dependent lipid peroxidation, uniquely links metabolic vulnerability with oxidative stress and is particularly relevant to hepatocytes given the liver's central role in iron handling and lipid metabolism.

Importantly, these RCD modalities are not mutually exclusive. Their temporal activation, cellular distribution, and inflammatory potential collectively determine whether the hepatic response to sepsis favors adaptive injury resolution or progresses toward uncontrolled inflammation, immune dysfunction, and multi-organ failure. Recognizing both the shared and distinct features of these death programs provides a clearer mechanistic framework for understanding SALI and for identifying stage- and cell-specific therapeutic targets.

3 Crosstalk and convergence among RCD pathways in SALI

While apoptosis, necroptosis, pyroptosis, and ferroptosis have traditionally been investigated as independent RCD programs, accumulating evidence indicates that these pathways rarely operate in isolation during SALI. Importantly, the liver represents a uniquely vulnerable organ in which intensive metabolic activity, abundant mitochondria, iron-rich physiology, and dense innate immune surveillance converge. Within this specialized microenvironment, hepatocytes and Kupffer cells engage distinct but interconnected RCD programs in response to septic insults. Rather than functioning as independent execution mechanisms, multiple RCD modalities are often co-activated simultaneously and engage in extensive molecular crosstalk, leading to signal amplification and pathway convergence that shape inflammatory liver injury. This section therefore focuses on the interconnected nature of RCD pathways in SALI, highlighting shared molecular nodes and cooperative mechanisms within the hepatic context.

3.1 Caspase-8: a molecular switch linking apoptosis, necroptosis, and pyroptosis

Caspase-8 serves as a central switch coordinating multiple RCD modalities. Under physiological conditions, it activates caspase-3/7

to initiate apoptosis while simultaneously cleaving RIPK1 and RIPK3 to suppress necroptosis. In the septic microenvironment, increased cFLIP expression restrains caspase-8 activation within death receptor complexes, suppressing apoptotic execution and reshaping downstream signaling. Under conditions of sustained caspase-8 inhibition, this shift may permit RIPK1–RIPK3 complex formation and increase susceptibility to necroptotic or other inflammatory cell death programs (67). When both apoptosis and necroptosis are blocked, caspase-8 serves as a scaffold that interacts with the ASC to activate NLRP3-dependent pyroptosis (68). Moreover, under specific stimuli such as *Yersinia* infection, caspase-8 directly cleaves GSDMD to trigger pyroptosis independent of caspase-1 (69).

3.2 NLRP3 inflammasome: a convergence hub of inflammatory RCD

The NLRP3 inflammasome acts as a key integrator of inflammatory cell death and plays an important role in SALI. Classically, it activates caspase-1 to cleave GSDMD in immune cells, leading to IL-1 β and IL-18 release during pyroptosis. Beyond this canonical role, NLRP3 interacts with other death pathways. During apoptosis, NLRP3 colocalizes with ASC and caspase-8 in mitochondria-associated speck-like complexes (70). In the absence of caspase-1, NLRP3 inflammasomes directly engage caspase-8 to initiate apoptosis and cytokine processing (71). Iron overload promotes NLRP3 activation through the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon gene (STING) pathway, while ROS generated by NLRP3 activation exacerbate lipid peroxidation, thereby linking inflammasome signaling to ferroptosis (72). Ferroptosis in Kupffer cells can contribute to liver injury by amplifying oxidative and inflammatory signals. Moreover, activation of the NLRP3 inflammasome in Kupffer cells directly contributes to hepatocyte death, as demonstrated in a Kupffer cell–hepatocyte co-culture model in which Kupffer cells isolated from *Nlrp3*-deficient mice induced significantly less hepatocyte death than their wild-type counterparts (73). Moreover, MLKL, a key effector of necroptosis, can also activate NLRP3 in macrophages, amplifying inflammation and forming a feedback loop between necroptosis and pyroptosis (74). These findings suggest that NLRP3 represents a pivotal node integrating inflammatory and death signals in SALI.

3.3 Lipid peroxidation: a shared effector connecting oxidative and inflammatory cell death

Lipid peroxidation represents a critical biochemical process that integrates oxidative stress with multiple RCD pathways in SALI. In polymicrobial sepsis models, hepatic lipid peroxidation is significantly increased and parallels enhanced hepatocyte apoptosis, implicating lipid peroxidation as a key contributor to sepsis-induced hepatocyte injury (75). Under septic stress, excessive ROS production promotes peroxidative damage to mitochondrial membrane, thereby facilitating Cyt-c release and initiating mitochondria-dependent apoptosis in hepatocytes (76). Beyond apoptosis, lipid peroxidation

intersects with inflammatory cell death pathways. During sepsis, lipid peroxidation drives pyroptosis through caspase-11-mediated GSDMD cleavage and phospholipase C gamma 1-dependent activation of GSDMD fragments (77). Notably, lipid peroxidation product can exert context-dependent regulatory effects on inflammasome signaling: 4-hydroxynonenal (4-HNE) inhibits NLRP3 inflammasome activation and macrophage pyroptosis by impairing NEK7–NLRP3 interactions (78), whereas the PUFA-derived lipid mediator resolving D1 suppresses caspase-1/GSDMD-dependent pyroptosis in the liver of septic mice (79). Ferroptosis, intrinsically characterized by iron-dependent lipid peroxidation, is particularly relevant to SALI given the liver's central role in iron storage and lipid metabolism (80). This process is counteracted by GPX4-dependent and -independent antioxidant defenses. Collectively, these findings highlight lipid peroxidation not merely as a downstream consequence of oxidative stress, but as a shared effector that both drives and fine-tunes the crosstalk among apoptotic, pyroptotic, and ferroptotic pathways in SALI.

From a translational perspective, recognizing lipid peroxidation as both a trigger and a modulator of RCD in SALI has important therapeutic implications. Antioxidant approaches that curb ROS-driven lipid peroxidation, iron chelation therapies that limit the labile iron pool fueling ferroptosis, and interventions enhancing GPX4-dependent or GPX4-independent lipid peroxide detoxification may collectively restrain systemic inflammatory amplification during sepsis. By reducing the release of DAMPs and pro-inflammatory lipid species from injured hepatocytes and hepatic macrophages, such strategies could plausibly attenuate cytokine storm propagation, preserve immune cell function, and mitigate downstream multi-organ injury. Therefore, modulation of lipid peroxidation emerges as a unifying therapeutic entry point linking hepatic protection with systemic immune homeostasis in sepsis.

3.4 Bile acid metabolism: a liver-specific modulator of RCD in sepsis

Bile acids are liver-derived metabolites that play essential roles in lipid digestion, metabolic homeostasis, and immune regulation. During sepsis, bile acid metabolism is profoundly disrupted and is increasingly recognized as a contributor to SALI (81). Excessive accumulation of bile acids has been shown to exert direct cytotoxic effects on hepatocytes and to activate inflammatory signaling cascades, thereby promoting multiple forms of cell death, including apoptosis, necrotic cell death, and pyroptosis (82). Experimental endotoxemia and polymicrobial sepsis models consistently demonstrate marked alterations in circulating and hepatic bile acid profiles, accompanied by cholestasis and hepatic inflammation. Notably, pharmacological activation of the bile acid receptor farnesoid X receptor (FXR) partially restores bile acid homeostasis and alleviates liver injury, underscoring the regulatory importance of bile acid signaling in SALI (83). Mechanistically, bile acids can function as DAMPs capable of activating NLRP3 inflammasome in macrophages, whereas FXR signaling negatively regulates NLRP3 activity and downstream inflammatory cytokine production (84). In addition to FXR, the bile acid receptor Takeda G

protein-coupled receptor 5 (TGR5) represents a critical liver-enriched immunometabolic sensor during sepsis. Recent evidence demonstrates that TGR5 expression is significantly upregulated in the liver and macrophages following bacterial infection and LPS challenge, indicating an adaptive hepatic response to septic stress (85). Activation of TGR5 not only drives the polarization of hepatic macrophages toward an anti-inflammatory phenotype but also suppresses the activation of the NLRP3 inflammasome, thereby mitigating hepatocyte pyroptosis and inflammatory damage (86). Clinically, patients with septic shock exhibit markedly elevated circulating bile acids levels, particularly in the presence of hepatic dysfunction. These alterations have been shown to be independently associated with increased short-term mortality and may serve as early biomarkers for risk stratification in critically ill patients (87). Given the liver's central role in bile acid synthesis, enterohepatic circulation, and bile acid receptor-mediated immunometabolic regulation, dysregulated bile acid metabolism is likely to exacerbate oxidative stress, mitochondrial dysfunction, inflammatory signaling, and RCD pathways in both hepatocytes and hepatic macrophages during SALI. Collectively, these findings establish bile acid metabolism as a liver-specific metabolic axis linking immunometabolic disturbance to inflammatory RCD during sepsis.

4 Signaling pathways orchestrating RCD and inflammation in SALI

While the preceding sections detailed the molecular mechanisms and crosstalk among distinct forms of RCD, these processes do not occur autonomously. Instead, the initiation and intensity of RCD are tightly governed by upstream signaling pathways that integrate inflammatory, oxidative, and metabolic disturbances during sepsis. Therefore, understanding how key intracellular signaling cascades orchestrate RCD and inflammation is essential for elucidating the pathogenesis of SALI.

Among the numerous signaling pathways implicated in SALI, phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), Nrf2, and nuclear factor κ -B (NF- κ B) were selected for focused discussion based on three considerations. First, these pathways represent distinct but complementary regulatory axes governing cell survival, oxidative stress responses, and inflammatory signaling—three central determinants of RCD fate in SALI. Second, accumulating evidence indicates that each of these pathways directly intersects with multiple RCD modalities, including apoptosis, pyroptosis, necroptosis, and ferroptosis, rather than regulating a single death program. Third, these signaling cascades are highly druggable and have been repeatedly validated in experimental SALI models, highlighting their translational relevance.

4.1 PI3K/Akt pathway: a cytoprotective modulator of hepatocyte survival

The PI3K/Akt pathway is a central signaling cascade regulating cell growth, metabolism, and survival (88). In sepsis, it exerts

protective effects by limiting excessive inflammatory cytokine release and enhancing stress adaptation. Inhibition of PI3K aggravates polymicrobial sepsis, whereas its activation mitigates sepsis-related morbidity and mortality (89).

In the context of SALI, PI3K/Akt activation protects hepatocytes from Fas- or TNF- α -induced apoptosis (90). Upstream regulators such as fibroblast growth factor 5 and thymic stromal lymphopoietin attenuate LPS-induced liver injury via PI3K/Akt-dependent anti-apoptotic and autophagic mechanisms (91, 92). Similarly, the long non-coding RNA LncRNA 220 modulates autophagy and apoptosis in Kupffer cells through the miR-5101/PI3K/Akt/mTOR axis (93).

Natural compounds including wedelolactone, aloe-emodin, and curcumin modulate PI3K/Akt signaling to suppress oxidative stress, ferroptosis, apoptosis, and inflammation (94–96). Interestingly, time-restricted feeding alleviates septic liver injury by remodeling gut microbiota, enriching *Lactobacillus murinus*, and activating PI3K/Akt/mTOR signaling to inhibit hepatocyte ferroptosis (97). Collectively, these findings establish the PI3K/Akt pathway as a crucial cytoprotective axis and an attractive therapeutic target for SALI.

4.2 Nrf2 pathway: master regulator of antioxidant and anti-ferroptotic defense

Nrf2 is a master transcriptional regulator of cellular antioxidant defense and redox balance (98). Under basal conditions, it is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (Keap1); oxidative stress promotes Nrf2 dissociation and nuclear translocation, where it binds antioxidant response elements (AREs) to induce cytoprotective genes (99).

During sepsis, Nrf2 activation suppresses excessive inflammation and improves host survival (100). In SALI, Nrf2 mitigates hepatic injury by repressing oxidative stress and inflammation, while Nrf2 deficiency aggravates liver injury (101). Mechanistically, Nrf2 inhibits ferroptosis through upregulation of SLC7A11, GPX4, and autophagy-related proteins (102). Pharmacological activators such as artemisitene and nobiletin alleviate SALI via Nrf2-mediated antioxidant and anti-ferroptotic signaling (103, 104). Furthermore, Nrf2 activation limits pyroptosis by suppressing NLRP3 inflammasome formation (42, 105, 106). Collectively, Nrf2 acts as a multifaceted guardian integrating antioxidant, anti-ferroptotic, and anti-pyroptotic responses in SALI.

4.3 NF- κ B signaling pathway: a central driver of inflammation and cell death

NF- κ B is a central transcription factor regulating inflammation, immunity, and cell fate decisions (107). Under resting conditions, NF- κ B is retained in the cytoplasm by Inhibitor of κ B (I κ B) proteins. Upon exposure to stimuli such as cytokines, LPS, or oxidative stress, I κ B is phosphorylated and degraded, enabling NF- κ B translocation to the nucleus, where it binds to target gene promoters and initiates transcription of inflammatory mediators (108).

Excessive activation of NF- κ B is a hallmark of sepsis and correlates with increased mortality and poor clinical outcomes (109). Accordingly, inhibition of NF- κ B signaling alleviates systemic inflammation and organ dysfunction. In SALI, activation

of the TLR4/MyD88/NF- κ B axis contributes to LPS-induced hepatocyte apoptosis (110). Golgi phosphoprotein 3 exacerbates endotoxemia-induced liver injury via inhibition of Akt/NF- κ B signaling, whereas its knockdown mitigates damage (111). Multiple agents—including neoastilbin, L-ascorbic acid 6-palmitate, rupatadine, and resveratrol—suppress NF- κ B to reduce oxidative stress, apoptosis, and inflammation (112–115). Thus, NF- κ B represents a pivotal proinflammatory driver linking immune dysregulation and cell death in SALI.

Collectively, these signaling pathways do not operate in isolation. PI3K/Akt increases cellular resilience to apoptotic and ferroptotic stress, Nrf2 sets antioxidant capacity and ferroptotic sensitivity, whereas NF- κ B amplifies inflammatory RCD programs such as pyroptosis and necroptosis. The dynamic balance among these pathways critically shapes whether hepatocytes and hepatic immune cells undergo adaptive survival, inflammatory death, or irreversible metabolic collapse during SALI progression. Importantly, emerging liver-targeted drug designs highlight the translational feasibility of modulating these inflammatory signaling pathways in SALI. For example, a camptothecin–bile acid conjugate exhibited pronounced hepatic targeting and markedly attenuated liver injury in septic mice by inhibiting NF- κ B signaling (116). This bile acid-based delivery strategy not only enhanced hepatic drug exposure but also reduced systemic toxicity, underscoring the importance of liver-specific targeting and hepatic metabolism in the development of effective therapies for SALI.

5 Conclusions and perspectives

SALI represents a multifactorial process driven by interconnected RCD pathways within the liver's unique immunometabolic environment. Apoptosis, necroptosis, pyroptosis, and ferroptosis form a dynamic and partially overlapping network that amplifies hepatic inflammation and dysfunction in sepsis. Crosstalk mediated by caspase-8, NLRP3 inflammasome, and lipid peroxidation integrates immune, metabolic, and oxidative stress signals. Meanwhile, the PI3K/Akt, Nrf2, and NF- κ B pathways orchestrate the balance between cell survival and death.

Future research should focus on (1) delineating temporal and cell-type-specific dynamics of RCD activation during sepsis progression (2); identifying liver-enriched immunometabolic regulators that modulate multiple RCD modalities; and (3) developing combinational therapies targeting shared signaling hubs to achieve hepatic protection while preserving systemic immune homeostasis. A deeper understanding of these networks will pave the way for precision interventions to restore hepatic and systemic immune homeostasis in sepsis.

Author contributions

KZ: Conceptualization, Investigation, Writing – original draft. NW: Investigation, Methodology, Writing – review & editing.

LW: Investigation, Writing – original draft. ZZ: Investigation, Writing – original draft. MG: Writing – original draft, Methodology. JZ: Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

- van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. *Nat Rev Immunol.* (2017) 17:407–20. doi: 10.1038/nri.2017.36
- Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet.* (2020) 395:200–11. doi: 10.1016/S0140-6736(19)32989-7
- Li C, Ji J, Shi T, Pan S, Jiang K, Jiang Y, et al. Establishment and validation of a risk prediction model for sepsis-associated liver injury in ICU patients: A retrospective cohort study. *Infect Drug Resist.* (2025) 18:1–13. doi: 10.2147/IDR.S489196
- Sun J, Zhang J, Wang X, Ji F, Ronco C, Tian J, et al. Gut-liver crosstalk in sepsis-induced liver injury. *Crit Care.* (2020) 24:614. doi: 10.1186/s13054-020-03327-1
- van der Poll T, Shankar-Hari M, Wiersinga WJ. The immunology of sepsis. *Immunity.* (2021) 54:2450–64. doi: 10.1016/j.immuni.2021.10.012
- Strnad P, Tacke F, Koch A, Trautwein C. Liver - guardian, modifier and target of sepsis. *Nat Rev Gastroenterol Hepatol.* (2016) 14:55–66. doi: 10.1038/nrgastro.2016.168
- Tang D, Kang R, Berghe TV, Vandenebeele P, Kroemer G. The molecular machinery of regulated cell death. *Cell Res.* (2019) 29:347–64. doi: 10.1038/s41422-019-0164-5
- Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. *Cell Death Differ.* (2018) 25:486–541. doi: 10.1038/s41418-017-0012-4
- Lu N, Qin H, Meng Z, Yu Y, Gao Q, Cheng Z, et al. Inhibiting apoptosis and GSDME-mediated pyroptosis attenuates hepatic injury in septic mice. *Arch Biochem Biophys.* (2024) 754:109923. doi: 10.1016/j.abb.2024.109923
- Abbas H, Derkaoui DK, Jeammet L, Adicéam E, Tiollier J, Sicard H, et al. Apoptosis inhibitor 5: A multifaceted regulator of cell fate. *Biomolecules.* (2024) 14:136. doi: 10.3390/biom14010136
- Xu X, Lai Y, Hua Z-C. Apoptosis and apoptotic body: disease message and therapeutic target potentials. *Biosci Rep.* (2019) 39:BSR20180992. doi: 10.1042/BSR20180992
- Ketelut-Carneiro N, Fitzgerald KA. Apoptosis, pyroptosis, and necroptosis—oh my! The many ways a cell can die. *J Mol Biol.* (2021) 434:167378. doi: 10.1016/j.jmb.2021.167378
- Werry F, Mazur E, Theyse LFH, Edlich F. Apoptosis regulation in osteoarthritis and the influence of lipid interactions. *Int J Mol Sci.* (2023) 24:13028. doi: 10.3390/ijms241713028
- Kudo H, Takahara T, Yata Y, Kawai K, Zhang W, Sugiyama T. Lipopolysaccharide triggered TNF- α -induced hepatocyte apoptosis in a murine non-alcoholic steatohepatitis model. *J Hepatol.* (2009) 51:168–75. doi: 10.1016/j.jhep.2009.02.032
- Wang Y, Weng L, Wu X, Du B. The role of programmed cell death in organ dysfunction induced by opportunistic pathogens. *Crit Care.* (2025) 29:43. doi: 10.1186/s13054-025-05278-x
- Chung C-S, Venet F, Chen Y, Jones LN, Wilson DC, Ayala CA, et al. Deficiency of Bid protein reduces sepsis-induced apoptosis and inflammation, while improving septic survival. *Shock.* (2010) 34:150–61. doi: 10.1097/SHK.0b013e3181cf70fb
- Qian W-J, Cheng Q-H. Endoplasmic reticulum stress-mediated apoptosis signal pathway is involved in sepsis-induced liver injury. *Int J Clin Exp Pathol.* (2017) 10:9990–7.
- Arunachalam AR, Samuel SS, Mani A, Maynard JP, Stayer KM, Dybbro E, et al. P2Y₂ purinergic receptor gene deletion protects mice from bacterial endotoxin and sepsis-associated liver injury and mortality. *Am J Physiol Gastrointest Liver Physiol.* (2023) 325:G471–G91. doi: 10.1152/ajpgi.00090.2023
- Yuan F-H, Chen Y-L, Zhao Y, Liu Z-M, Nan C-C, Zheng B-L, et al. microRNA-30a inhibits the liver cell proliferation and promotes cell apoptosis through the JAK/STAT signaling pathway by targeting SOCS-1 in rats with sepsis. *J Cell Physiol.* (2019) 234:17839–53. doi: 10.1002/jcp.28410
- Zhou Y-P, Xia Q. Inhibition of miR-103a-3p suppresses lipopolysaccharide-induced sepsis and liver injury by regulating FBXW7 expression. *Cell Biol Int.* (2020) 44:1798–810. doi: 10.1002/cbin.11372
- Matouk AI, El-Daly M, Habib HA, Senousy S, Naguib Abdel Hafez SM, Kasem AW, et al. Protective effects of menthol against sepsis-induced hepatic injury: Role of mediators of hepatic inflammation, apoptosis, and regeneration. *Front Pharmacol.* (2022) 13:952337. doi: 10.3389/fphar.2022.952337
- Xiong X, Ren Y, Cui Y, Li R, Wang C, Zhang Y. Obeticholic acid protects mice against lipopolysaccharide-induced liver injury and inflammation. *BioMed Pharmacother.* (2017) 96:1292–8. doi: 10.1016/j.biopha.2017.11.083
- Tang X, Ning J, Zhao Y, Feng S, Shao L, Liu T, et al. Intestine-derived fibroblast growth factor 19 alleviates lipopolysaccharide-induced liver injury by regulating bile acid homeostasis and directly improving oxidative stress. *J Intensive Med.* (2024) 5:79–88. doi: 10.1016/j.jointm.2024.06.003
- Chen Y, Ren W, Wang Q, He Y, Ma D, Cai Z. The regulation of necroptosis by ubiquitylation. *Apoptosis.* (2022) 27:668–84. doi: 10.1007/s10495-022-01755-8
- Qu M, Wang Y, Qiu Z, Zhu S, Guo K, Chen W, et al. Necroptosis, pyroptosis, ferroptosis in sepsis and treatment. *Shock.* (2022) 57:161–71. doi: 10.1097/SHK.0000000000001936
- Khan I, Yousef A, Chesnokov M, Hong L, Chefetz I. A decade of cell death studies: Breathing new life into necroptosis. *Pharmacol Ther.* (2020) 220:107717. doi: 10.1016/j.pharmthera.2020.107717
- Baker MODG, Shanmugam N, Pham CLL, Ball SR, Sierecki E, Gambin Y, et al. The RHIM of the immune adaptor protein TRIF forms hybrid amyloids with other necroptosis-associated proteins. *Molecules.* (2022) 27:3382. doi: 10.3390/molecules27113382
- Meng Y, Meng S, Zhang Y, Song Y, Wang E, Wang G, et al. The protective effect of dexmedetomidine on the liver injury in sepsis through inhibition of necroptosis. *Shock.* (2024) 61:424–32. doi: 10.1097/SHK.0000000000002303
- Xu Q, Guo J, Li X, Wang Y, Wang D, Xiao K, et al. Necroptosis underlies hepatic damage in a piglet model of lipopolysaccharide-induced sepsis. *Front Immunol.* (2021) 12:633830. doi: 10.3389/fimmu.2021.633830
- Qian Z, Shuying W, Ranran D. Inhibitory effects of JQ1 on listeria monocytogenes-induced acute liver injury by blocking BRD4/RIPK1 axis. *BioMed Pharmacother.* (2020) 125:109818. doi: 10.1016/j.biopha.2020.109818
- Kitur K, Wachtel S, Brown A, Wickersham M, Paulino F, Peñaloza HF, et al. Necroptosis promotes staphylococcus aureus clearance by inhibiting excessive inflammatory signaling. *Cell Rep.* (2016) 16:2219–30. doi: 10.1016/j.celrep.2016.07.039
- Zhang Q, Wei S, Lu J, Fu W, Chen H, Huang Q, et al. Necrostatin-1 accelerates time to death in a rat model of cecal ligation and puncture and massively increases hepatocyte caspase-3 cleavage. *Am J Physiol Gastrointest Liver Physiol.* (2019) 316:G551–G61. doi: 10.1152/ajpgi.00175.2018
- Li W, Sun J, Zhou X, Lu Y, Cui W, Miao L. Mini-review: GSDME-mediated pyroptosis in diabetic nephropathy. *Front Pharmacol.* (2021) 12:780790. doi: 10.3389/fphar.2021.780790
- Broz P, Pelegrin P, Shao F. The gasdermins, a protein family executing cell death and inflammation. *Nat Rev Immunol.* (2019) 20:143–57. doi: 10.1038/s41577-019-0228-2
- Rao Z, Zhu Y, Yang P, Chen Z, Xia Y, Qiao C, et al. Pyroptosis in inflammatory diseases and cancer. *Theranostics.* (2022) 12:4310–29. doi: 10.7150/thno.71086
- Kayagaki N, Stowe IB, Lee BL, O'Rourke K, Anderson K, Warming S, et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. *Nature.* (2015) 526:666–71. doi: 10.1038/nature15541
- Bhat AA, Thapa R, Afzal O, Agrawal N, Almalki WH, Kazmi I, et al. The pyroptotic role of Caspase-3/GSDME signalling pathway among various cancer: A Review. *Int J Biol Macromol.* (2023) 242:124832. doi: 10.1016/j.ijbiomac.2023.124832
- Demarco B, Graczyk JP, Bjanec E, Le Roy D, Tonnu W, Assenmacher C-A, et al. Caspase-8-dependent gasdermin D cleavage promotes antimicrobial defense but confers susceptibility to TNF-induced lethality. *Sci Adv.* (2020) 6:eabc3465. doi: 10.1126/sciadv.abc3465
- Liu J, Du S, Kong Q, Zhang X, Jiang S, Cao X, et al. HSPA12A attenuates lipopolysaccharide-induced liver injury through inhibiting caspase-11-mediated hepatocyte pyroptosis via PGC-1 α -dependent acylolactone expression. *Cell Death Differ.* (2020) 27:2651–67. doi: 10.1038/s41418-020-0536-x
- Wang T, Zhong H, Zhang W, Wen J, Yi Z, Li P, et al. STAT5a induces endotoxin tolerance by alleviating pyroptosis in kupffer cells. *Mol Immunol.* (2020) 122:28–37. doi: 10.1016/j.molimm.2020.03.016
- Kuang L, Wu Y, Shu J, Yang J, Zhou H, Huang X. Pyroptotic Macrophage-Derived Microvesicles Accelerate Formation of Neutrophil Extracellular Traps via GSDMD-N-expressing Mitochondrial Transfer during Sepsis. *Int J Biol Sci.* (2024) 20:733–50. doi: 10.7150/ijbs.87646
- Yang W, Tao K, Zhang P, Chen X, Sun X, Li R. Maresin 1 protects against lipopolysaccharide/d-galactosamine-induced acute liver injury by inhibiting macrophage pyroptosis and inflammatory response. *Biochem Pharmacol.* (2021) 195:114863. doi: 10.1016/j.bcp.2021.114863
- Zhao Y-Y, Wu D-M, He M, Zhang F, Zhang T, Liu T, et al. Samotolisib attenuates acute liver injury through inhibiting caspase-11-mediated pyroptosis via regulating E3 ubiquitin ligase nedd4. *Front Pharmacol.* (2021) 12:726198. doi: 10.3389/fphar.2021.726198
- Li Q, Tan Y, Chen S, Xiao X, Zhang M, Wu Q, et al. Irisin alleviates LPS-induced liver injury and inflammation through inhibition of NLRP3 inflammasome and NF- κ B signaling. *J Recept Signal Transduct Res.* (2020) 41:294–303. doi: 10.1080/10799893.2020.1808675
- Zhu L, Hu M, Xu H, Xu H, Ren B, Xu R, et al. The key players of inflammasomes and pyroptosis in sepsis-induced pathogenesis and organ dysfunction. *Front Pharmacol.* (2025) 16:1586364. doi: 10.3389/fphar.2025

46. Li F, Han X, Wu C, He J, Liu H, Li S, et al. Evaluation of immune and pyroptosis status in a model of sepsis-induced secondary pneumonia. *Int Immunopharmacol.* (2024) 140:112835. doi: 10.1016/j.intimp.2024.112835
47. Islam MM, Watanabe E, Salma U, Ozaki M, Irahara T, Tanabe S, et al. Immunoadjuvant therapy in the regulation of cell death in sepsis: recent advances and future directions. *Front Immunol.* (2024) 15:1493214. doi: 10.3389/fimmu.2024.1493214
48. Liang D, Minikes AM, Jiang X. Ferroptosis at the intersection of lipid metabolism and cellular signaling. *Mol Cell.* (2022) 82:2215–27. doi: 10.1016/j.molcel.2022.03.022
49. Tang D, Chen X, Kang R, Kroemer G. Ferroptosis: molecular mechanisms and health implications. *Cell Res.* (2020) 31:107–25. doi: 10.1038/s41422-020-00441-1
50. Chen F, Kang R, Tang D, Liu J. Ferroptosis: principles and significance in health and disease. *J Hematol Oncol.* (2024) 17:41. doi: 10.1186/s13045-024-01564-3
51. Stockwell BR. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. *Cell.* (2022) 185:2401–21. doi: 10.1016/j.cell.2022.06.003
52. Liu Y, Wan Y, Jiang Y, Zhang L, Cheng W. GPX4: The hub of lipid oxidation, ferroptosis, disease and treatment. *Biochim Biophys Acta Rev Cancer.* (2023) 1878:188890. doi: 10.1016/j.bbcan.2023.188890
53. Zhou P, Zhang S, Wang M, Zhou J. The induction mechanism of ferroptosis, necroptosis, and pyroptosis in inflammatory bowel disease, colorectal cancer, and intestinal injury. *Biomolecules.* (2023) 13:820. doi: 10.3390/biom13050820
54. Mishima E, Ito J, Wu Z, Nakamura T, Wahida A, Doll S, et al. A non-canonical vitamin K cycle is a potent ferroptosis suppressor. *Nature.* (2022) 608:778–83. doi: 10.1038/s41586-022-05022-3
55. Larsen R, Gozzelino R, Jeney V, Tokaji L, Bozza FA, Japiassú AM, et al. A central role for free heme in the pathogenesis of severe sepsis. *Sci Transl Med.* (2010) 2:51ra71. doi: 10.1126/scitranslmed.3001118
56. Janz DR, Bastarache JA, Peterson JF, Sills G, Wickersham N, May AK, et al. Association between cell-free hemoglobin, acetaminophen, and mortality in patients with sepsis: an observational study. *Crit Care Med.* (2013) 41:784–90. doi: 10.1097/CCM.0b013e3182741a54
57. Bünger V, Scholz S, Russ M, Weber-Carstens S, Graw JA. Hemolysis, hemolytic markers, and mortality in sepsis: a scoping review. *Intensive Care Med Exp.* (2025) 13:79. doi: 10.1186/s40635-025-00786-0
58. Zhou HT, Huang J, Liu YK, Wang JH, Wang J. The emerging role of ferroptosis in the pathological development and progression of sepsis. *Mil Med Res.* (2025) 12:81. doi: 10.1186/s40779-025-00665-5
59. Wang Y, Wang T, Xiang Q, Li N, Wang J, Liu J, et al. GPR116 promotes ferroptosis in sepsis-induced liver injury by suppressing system Xc-/GSH/GPX4. *Cell Biol Toxicol.* (2023) 39:3015–30. doi: 10.1007/s10565-023-09815-8
60. Wang J, Zhu Q, Li R, Zhang J, Ye X, Li X. YAP1 protects against septic liver injury via ferroptosis resistance. *Cell Biosci.* (2022) 12:163. doi: 10.1186/s13578-022-00902-7
61. Wu W, Wang J, Chen J, Lu J, Lao Y, Huang K, et al. MFG-E8 has guiding significance for the prognosis and treatment of sepsis. *Sci Rep.* (2022) 12:20916. doi: 10.1038/s41598-022-25601-8
62. Wei S, Bi J, Yang L, Zhang J, Wan Y, Chen X, et al. Serum irislin levels are decreased in patients with sepsis, and exogenous irislin suppresses ferroptosis in the liver of septic mice. *Clin Transl Med.* (2020) 10:e173. doi: 10.1002/ctm2.173
63. Wang H, Su Z, Qian Y, Shi B, Li H, An W, et al. Pentraxin-3 modulates hepatocyte ferroptosis and the innate immune response in LPS-induced liver injury. *Mol Biomed.* (2024) 5:68. doi: 10.1186/s43556-024-00227-6
64. Feng L, Cui J, Chen W, Zhu L, Li P, Zhou H, et al. Nrg4 secreted by brown adipose tissue suppresses ferroptosis of sepsis-induced liver injury. *Inflammation.* (2025) 48:2783–801. doi: 10.1007/s10753-024-02230-z
65. Guo Y, Chen H, Sun J, Zhang J, Yin Y. Maresin1 inhibits ferroptosis via the nrf2/SLC7A11/GPX4 pathway to protect against sepsis-induced acute liver injury. *J Inflammation Res.* (2024) 17:11041–53. doi: 10.2147/JIR.S498775
66. Zhang H, Shi H, Li X, Zhou S, Song X, Ma N, et al. Quercetin alleviates LPS/iE-DAP-induced liver injury by suppressing ferroptosis via regulating ferritinophagy and intracellular iron efflux. *Redox Biol.* (2025) 81:103557. doi: 10.1016/j.redox.2025.103557
67. Davidovich P, Higgins CA, Najda Z, Longley DB, Martin SJ. cFLIPL acts as a suppressor of TRAIL- and Fas-initiated inflammation by inhibiting assembly of caspase-8/FADD/RIPK1 NF- κ B-activating complexes. *Cell Rep.* (2023) 42:113476. doi: 10.1016/j.celrep.2023.113476
68. Fritsch M, Günther SD, Schwarzer R, Albert M-C, Schorn F, Werthenbach JP, et al. Caspase-8 is the molecular switch for apoptosis, necroptosis and pyroptosis. *Nature.* (2019) 575:683–7. doi: 10.1038/s41586-019-1770-6
69. Sarhan J, Liu BC, Muendlein HI, Li P, Nilson R, Tang AY, et al. Caspase-8 induces cleavage of gasdermin D to elicit pyroptosis during *Yersinia* infection. *Proc Natl Acad Sci U S A.* (2018) 115:E10888–E97. doi: 10.1073/pnas.1809548115
70. Chung H, Vilaysane A, Lau A, Stahl M, Morampudi V, Bondzi-Simpson A, et al. NLRP3 regulates a non-canonical platform for caspase-8 activation during epithelial cell apoptosis. *Cell Death Differ.* (2016) 23:1331–46. doi: 10.1038/cdd.2016.14
71. Antonopoulos C, Russo HM, El Sanadi C, Martin BN, Li X, Kaiser WJ, et al. Caspase-8 as an effector and regulator of NLRP3 inflammasome signaling. *J Biol Chem.* (2015) 290:20167–84. doi: 10.1074/jbc.M115.652321
72. Gupta U, Ghosh S, Wallace CT, Shang P, Xin Y, Nair AP, et al. Increased LCN2 (lipocalin 2) in the RPE decreases autophagy and activates inflammasome-ferroptosis processes in a mouse model of dry AMD. *Autophagy.* (2022) 19:92–111. doi: 10.1080/15548627.2022.2062887
73. Li R, Wei R, Liu C, Zhang K, He S, Liu Z, et al. Heme oxygenase 1-mediated ferroptosis in Kupffer cells initiates liver injury during heat stroke. *Acta Pharm Sin B.* (2024) 14:3983–4000. doi: 10.1016/j.apsb.2024.05.007
74. Conos SA, Chen KW, De Nardo D, Hara H, Whitehead L, Núñez G, et al. Active MLKL triggers the NLRP3 inflammasome in a cell-intrinsic manner. *Proc Natl Acad Sci U S A.* (2017) 114:E961–E9. doi: 10.1073/pnas.1613305114
75. Van Wyngene L, Vanderhaeghen T, Timmermans S, Vandewalle J, Van Looveren K, Souffriau J, et al. Hepatic PPAR α function and lipid metabolic pathways are dysregulated in polymicrobial sepsis. *EMBO Mol Med.* (2020) 12:e11319. doi: 10.15252/emmm.201911319
76. Fei M, Xu Y, Jin P, Wang Y, Zhou M. Mitochondrial dysfunction in sepsis-induced liver injury: from pathophysiology to preclinical therapeutic targets. *J Transl Med.* (2025) 23:1339. doi: 10.1186/s12967-025-07369-3
77. Kang R, Zeng L, Zhu S, Xie Y, Liu J, Wen Q, et al. Lipid peroxidation drives gasdermin D-mediated pyroptosis in lethal polymicrobial sepsis. *Cell Host Microbe.* (2018) 24:97–108. doi: 10.1016/j.chom.2018.05.009
78. Hsu CG, Chávez CL, Zhang C, Sowden M, Yan C, Berk BC. The lipid peroxidation product 4-hydroxynonenal inhibits NLRP3 inflammasome activation and macrophage pyroptosis. *Cell Death Differ.* (2022) 29:1790–803. doi: 10.1038/s41418-022-00966-5
79. Zhang W, Bhandari S, Ding Y, Luo J, Feng B, Jiang Y, et al. Polyunsaturated fatty acid-derived lipid mediator Resolvin D1 alleviates sepsis-induced disseminated intravascular coagulation via Caspase-1/Gasdermin D pyroptotic pathway. *Clin Nutr.* (2024) 43:1372–83. doi: 10.1016/j.clnu.2024.04.020
80. Hino K, Nishina S, Yanatori I. Ferroptosis: biology and role in liver disease. *J Gastroenterol.* (2025) 60:1339–61. doi: 10.1007/s00535-025-02300-5
81. Ghenu MI, Dragoş D, Manea MM, Ionescu D, Negreanu L. Pathophysiology of sepsis-induced cholestasis: A review. *JGH Open.* (2022) 6:378–87. doi: 10.1002/jgh3.12771
82. Fuchs CD, Trauner M. Role of bile acids and their receptors in gastrointestinal and hepatic pathophysiology. *Nat Rev Gastroenterol Hepatol.* (2022) 19:432–50. doi: 10.1038/s41575-021-00566-7
83. Wang J, Ma L, An Y, Ge Y, Xu D, Mao E. Protective effect of obeticholic acid on sepsis-induced liver dysfunction via regulating bile acid homeostasis. *Pharm (Basel).* (2025) 18:763. doi: 10.3390/ph18050763
84. Hao H, Cao L, Jiang C, Che Y, Zhang S, Takahashi S, et al. Farnesoid X receptor regulation of the NLRP3 inflammasome underlies cholestasis-associated sepsis. *Cell Metab.* (2017) 25:856–867.e5. doi: 10.1016/j.cmet.2017.03.007
85. Reich M, Franz T, Xu HC, Philippski P, Stindt J, Freier S, et al. Bile acid receptor Tgr5 prevents macrophage hyperinflammation during bacterial sepsis through metabolic and epigenetic silencing. *iScience.* (2025) 28:113929. doi: 10.1016/j.isci.2025.113929
86. Yuexiang Y, Zhiwei R, Li B, Qing W, Chunzheng L, Zetian W, et al. TCDCa inhibits pyroptosis to alleviate sepsis-related acute hepatic injury via activating TGR5. *Front Immunol.* (2025) 16:1706041. doi: 10.3389/fimmu.2025.1706041
87. Horvatis T, Drolz A, Rutter K, Roedl K, Langouche L, Van den Berghe G, et al. Circulating bile acids predict outcome in critically ill patients. *Ann Intensive Care.* (2017) 7:48. doi: 10.1186/s13613-017-0272-7
88. Yang J, Nie J, Ma X, Wei Y, Peng Y, Wei X. Targeting PI3K in cancer: mechanisms and advances in clinical trials. *Mol Cancer.* (2019) 18:26. doi: 10.1186/s12943-019-0954-x
89. Williams DL, Ozment-Skelton T, Li C. Modulation of the phosphoinositide 3-kinase signaling pathway alters host response to sepsis, inflammation, and ischemia/reperfusion injury. *Shock.* (2006) 25:432–9. doi: 10.1097/01.shk.0000209542.76305.55
90. Liu W, Jing Z-T, Xue C-R, Wu S-X, Chen W-N, Lin X-J, et al. PI3K/AKT inhibitors aggravate death receptor-mediated hepatocyte apoptosis and liver injury. *Toxicol Appl Pharmacol.* (2019) 381:114729. doi: 10.1016/j.taap.2019.114729
91. Cui S, Li Y, Zhang X, Wu B, Li M, Gao J, et al. Fibroblast growth factor 5 overexpression ameliorated lipopolysaccharide-induced apoptosis of hepatocytes through regulation of the phosphoinositide-3-kinase/protein kinase B pathway. *Chin (Engl).* (2022) 135:2859–68. doi: 10.1097/CM9.0000000000002540
92. Wang H, Zhu J, Wei L, Wu S, Shang L, Ye X, et al. TSLP protects against sepsis-induced liver injury by inducing autophagy via activation of the PI3K/Akt/STAT3 pathway. *Pathol Res Pract.* (2022) 236:153979. doi: 10.1016/j.prp.2022.153979
93. Yang Y, Tian T, Li S, Li N, Luo H, Jiang Y. LncRNA 220: A Novel Long Non-Coding RNA Regulates Autophagy and Apoptosis in Kupffer Cells via the miR-5101/PI3K/AKT/mTOR Axis in LPS-Induced Endotoxemic Liver Injury in Mice. *Int J Mol Sci.* (2023) 24:11210. doi: 10.3390/ijms241311210

94. Yin Y, Mu F, Zhang L, Zhao J, Gong R, Yin Y, et al. Wedelolactone activates the PI3K/AKT/NRF2 and SLC7A11/GPX4 signalling pathways to alleviate oxidative stress and ferroptosis and improve sepsis-induced liver injury. *J Ethnopharmacol.* (2025) 344:119557. doi: 10.1016/j.jep.2025.119557
95. Gao H, Ren Y, Liu C. Aloe-emodin suppresses oxidative stress and inflammation via a PI3K-dependent mechanism in a murine model of sepsis. *Evid Based Complement Alternat Med.* (2022) 2022:9697887. doi: 10.1155/2022/9697887
96. Zhong W, Qian K, Xiong J, Ma K, Wang A, Zou Y. Curcumin alleviates lipopolysaccharide induced sepsis and liver failure by suppression of oxidative stress-related inflammation via PI3K/AKT and NF- κ B related signaling. *BioMed Pharmacother.* (2016) 83:302–13. doi: 10.1016/j.biopha.2016.06.036
97. Hu J-J, Deng F, Sun Q-S, Xiong Q-M, Min Y, Feng S-Y, et al. Time-restricted feeding protects against septic liver injury by reshaping gut microbiota and metabolite 3-hydroxybutyrate. *Gut Microbes.* (2025) 17:2486515. doi: 10.1080/19490976.2025.2486515
98. Bellezza I, Giambanco I, Minelli A, Donato R. Nrf2-Keap1 signaling in oxidative and reductive stress. *Biochim Biophys Acta Mol Cell Res.* (2018) 1865:721–33. doi: 10.1016/j.bbamcr.2018.02.010
99. Liu S, Pi J, Zhang Q. Signal amplification in the KEAP1-NRF2-ARE antioxidant response pathway. *Redox Biol.* (2022) 54:102389. doi: 10.1016/j.redox.2022.102389
100. Kong X, Thimmulappa R, Craciun F, Harvey C, Singh A, Kombairaju P, et al. Enhancing Nrf2 pathway by disruption of Keap1 in myeloid leukocytes protects against sepsis. *Am J Respir Crit Care Med.* (2011) 184:928–38. doi: 10.1164/rccm.201102-0271OC
101. Li L, Zhang Q, Zhang X, Xu X, Wang X, Huang X, et al. Protective effects of Nrf2 against sepsis-induced hepatic injury. *Life Sci.* (2021) 282:119807. doi: 10.1016/j.lfs.2021.119807
102. Liu J, Huang C, Liu J, Meng C, Gu Q, Du X, et al. Nrf2 and its dependent autophagy activation cooperatively counteract ferroptosis to alleviate acute liver injury. *Pharmacol Res.* (2022) 187:106563. doi: 10.1016/j.phrs.2022.106563
103. Huang W, Chen H, He Q, Xie W, Peng Z, Ma Q, et al. Nobiletin protects against ferroptosis to alleviate sepsis-associated acute liver injury by modulating the gut microbiota. *Food Funct.* (2023) 14:7692–704. doi: 10.1039/d3fo1684f
104. Zhao C, Xiao C, Feng S, Bai J. Artemisitene Alters LPS-Induced Oxidative stress, inflammation and Ferroptosis in Liver Through Nrf2/HO-1 and NF- κ B Pathway. *Front Pharmacol.* (2023) 14:1177542. doi: 10.3389/fphar.2023.1177542
105. Zhou P, Yang L, Li R, Yin Y, Xie G, Liu X, et al. IRG1/itaconate alleviates acute liver injury in septic mice by suppressing NLRP3 expression and its mediated macrophage pyroptosis via regulation of the Nrf2 pathway. *Int Immunopharmacol.* (2024) 135:112277. doi: 10.1016/j.intimp.2024.112277
106. Hong M-K, Hu L-L, Zhang Y-X, Xu Y-L, Liu X-Y, He P-K, et al. 6-Gingerol ameliorates sepsis-induced liver injury through the Nrf2 pathway. *Int Immunopharmacol.* (2020) 80:106196. doi: 10.1016/j.intimp.2020.106196
107. Yu H, Lin L, Zhang Z, Zhang H, Hu H. Targeting NF- κ B pathway for the therapy of diseases: mechanism and clinical study. *Signal Transduct Target Ther.* (2020) 5:209. doi: 10.1038/s41392-020-00312-6
108. Li W, Li D, Chen Y, Abudou H, Wang H, Cai J, et al. Classic signaling pathways in alveolar injury and repair involved in sepsis-induced ALI/ARDS: new research progress and prospect. *Dis Markers.* (2022) 2022:6362344. doi: 10.1155/2022/6362344
109. Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, et al. NF- κ B in biology and targeted therapy: new insights and translational implications. *Signal Transduct Target Ther.* (2024) 9:53. doi: 10.1038/s41392-024-01757-9
110. Chen S-N, Tan Y, Xiao X-C, Li Q, Wu Q, Peng Y-Y, et al. Deletion of TLR4 attenuates lipopolysaccharide-induced acute liver injury by inhibiting inflammation and apoptosis. *Acta Pharmacol Sin.* (2021) 42:1610–9. doi: 10.1038/s41401-020-00597-x
111. Dusabimana T, Je J, Yun SP, Kim HJ, Kim H, Park SW. GOLPH3 promotes endotoxemia-induced liver and kidney injury through Golgi stress-mediated apoptosis and inflammatory response. *Cell Death Dis.* (2023) 14:458. doi: 10.1038/s41419-023-05975-x
112. Xu R, Wang D, Shao Z, Li X, Cao Q. Neostilbin ameliorates sepsis-induced liver and kidney injury by blocking the TLR4/NF- κ B pathway. *Histol Histopathol.* (2024) 39:1329–42. doi: 10.14670/HH-18-719
113. Liu L, Lin L, Wang Y, Yan X, Li R, He M, et al. L-AP alleviates liver injury in septic mice by inhibiting macrophage activation via suppressing NF- κ B and NLRP3 inflammasome/caspase-1 signal pathways. *J Agric Food Chem.* (2024) 72:8460–75. doi: 10.1021/acs.jafc.3c02781
114. Okan A, Doğançiyiğit Z, Yılmaz S, Uçar S, Arıkan Söylemez ES, Attar R. Evaluation of the protective role of resveratrol against sepsis caused by LPS via TLR4/NF- κ B/TNF- α signaling pathways: Experimental study. *Cell Biochem Funct.* (2023) 41:423–33. doi: 10.1002/cbf.3790
115. Sakr AG, Kafk HE, El-Kashef DH. Rupatadine modulates TLR4/MYD88/NF- κ B and AKT/PI3K signaling pathways, attenuating sepsis-induced liver injury in mice. *Eur J Pharmacol.* (2025) 1002:177873. doi: 10.1016/j.ejphar.2025.177873
116. Xiao LX, Qi L, Zhang XL, Zhou YQ, Yue HL, Yu ED, et al. Liver injury in septic mice were suppressed by a camptothecin-bile acid conjugate via inhibiting NF- κ B signaling pathway. *Life Sci.* (2020) 257:118130. doi: 10.1016/j.lfs.2020.118130