Perioperative Precision Medicine

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REVIEW ARTICLE

Dysregulated cell death and inflammation in perioperative medicine: Mechanisms and therapeutic opportunities

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Received October 3, 2025; Accepted February 28, 2026; Published March 31, 2026

DOI: 10.61189/775612vwvmhm

Abstract

Cell death is a fundamental process influencing tissue homeostasis and recovery following surgical trauma. In the perioperative context, regulated cell death aids in clearing damaged cells and initiating repair. However, excessive or dysregulated cell death—often exacerbated by ischemia-reperfusion injury, surgical stress, and anesthetic agents—can trigger intense inflammatory responses, leading to complications such as postoperative organ dysfunction (e.g., acute lung injury, delirium, and myocardial injury), impaired wound healing, and increased risk of infections. Mitochondrial dysfunction, a key contributor to these processes, releases damage-associated molecular patterns, further amplifying perioperative inflammation. Emerging evidence suggests that modulating specific cell death pathways (e.g., apoptosis, pyroptosis, necroptosis) and associated inflammatory signaling (e.g., via NLRP3 inflammasome or TLR4 inhibition) may offer novel strategies to improve perioperative outcomes. This review explores the interplay between cell death and inflammation, with emphasis on perioperative relevance, and discusses emerging therapeutic targets that may facilitate precision medicine in surgical patients.

Keywords: Cell death, Perioperative medicine, Inflammation, Ischemia-reperfusion injury, Damage-associated molecular patterns, Precision medicine, Organ protection

1 INTRODUCTION

The interaction network of cell death and inflammation is an important and rapidly developing field in current biomedical research. This interplay not only plays a crucial role in maintaining tissue homeostasis but also is central to the pathogenesis and progression of multiple diseases [1]. It represents a critical determinant of patient outcomes in the perioperative period. Surgical trauma, anesthesia, ischemia-reperfusion injury, and blood loss can disrupt cellular homeostasis, triggering programmed cell death pathways and robust inflammatory responses. While these processes are essential for tissue repair and defense, their dysregulation contributes significantly to postoperative complications, including acute kidney injury, acute respiratory distress syndrome, sepsis, postoperative cognitive dysfunction (POCD), and impaired wound healing. Cell death and inflammation are key physiological processes by which organisms respond to internal and external stimuli, and the complex relationship between the two has profound implications for both health and disease. Cell death, once simply

considered a way for organisms to clear useless or damaged cells, is now understood to be a highly regulated process that includes various distinct forms, such as apoptosis, necroptosis, pyroptosis, ferroptosis, and cuproptosis [2]. These modes of cell death not only differ in morphological and biochemical characteristics, but also play different roles in the regulation of inflammatory reactions [3]. For example, apoptosis is generally considered immunologically silent, and can be removed by efficient efferocytosis without triggering an inflammatory reaction. However, apoptotic cells can also release damage-associated molecular patterns (DAMPs), thereby activating immune responses. Studies have shown that cell death can affect inflammatory reactions through various mechanisms [4, 5]. On the one hand, DAMPs released by cell death can activate pattern recognition receptors (PRRs), thereby initiating inflammatory signaling pathways and promoting the production and release of inflammatory cytokines. On the other hand, inflammatory cytokines, such as TNF-α and interferons, can directly induce cell death, forming a positive feedback loop that exacerbates inflammatory reactions and tissue injury. Cell death can be both a trigger for inflammation and a result of inflammatory reactions, and this dual role leads to the complexity of interaction networks.

In perioperative medicine, the balance between beneficial and detrimental cell death is delicate. Apoptosis, for instance, typically resolves without inflammation, but impaired clearance of apoptotic cells can lead to secondary necrosis and DAMP release. Conversely, highly inflammatory death pathways like pyroptosis and necroptosis are increasingly recognized as key drivers of organ injury following surgical stress. Mitochondria, central to cellular energetics, also act as crucial signaling hubs; perioperative insults (e.g., hypoxia, oxidative stress) can cause mitochondrial dysfunction, promoting DAMP release (e.g., mtDNA, ATP) and activating innate immune receptors (e.g., TLR9, NLRP3). This initiates a cascade of pro-inflammatory cytokine production (e.g., IL-1β, IL-18, TNF-α), leading to further tissue damage and a potential cycle of inflammation and cell death.

Although there is a preliminary understanding of the interaction between cell death and inflammation, the specific molecular mechanisms and signaling networks remain incompletely understood. In particular, current research still lacks systematic integration regarding how various forms of cell death synergistically affect inflammatory reactions, the specific mechanisms of action of cell death and inflammation in different diseases, and how these networks temporally and spatially regulate the onset and pathological progression of inflammation [6]. Exploring the contribution of different cell death mechanisms to inflammatory regulatory networks and their potential targets will help to more comprehensively understand inflammation-related diseases and provide a theoretical basis for developing new therapeutic methods. Simultaneously, understanding the specific roles of different cell death modes and their complex crosstalk with inflammatory signals in the perioperative context is crucial. This knowledge paves the way for novel therapeutic strategies aimed at modulating these pathways to protect vulnerable organs, mitigate excessive inflammation, and promote recovery.

This review systematically analyzes cell death (apoptosis, pyroptosis, necroptosis, etc.) and the dynamic interaction mechanisms of inflammatory reactions, focusing on the spatiotemporal patterns of specific DAMPs (e.g., High Mobility Group Box 1 [HMGB1], mtDNA) that are released by different death pathways and that activate PRRs (TLR4/NLRP3), and elucidating the signal transduction logic of the "DAMPs-PRRs-inflammatory cascade". For sepsis, autoimmune diseases, and metabolic diseases, it deeply analyzes the cascade effects of key pathway imbalances such as NETosis triggering type I interferon storms, GSDMD-mediated IL-1β self-amplification cycles, and lipotoxicity-induced death mode switching, combining spatial transcriptomics and single-cell metabolomics technologies to reveal organ microenvironment specificity. Based on this, this review critically evaluates the Janus-faced nature of targeted intervention strategies (such as RIPK1 inhibitors), explores the mechanisms by which cell death and inflammation lead to perioperative pathology, emphasizes their clinical relevance, and validates their therapeutic potential in alleviating sepsis-induced multiple organ failure and chronicization of autoimmune diseases.

2 MOLECULAR MECHANISMS OF CELL DEATH

Since the phenomenon of cell death was first described in the 19th century, the field has undergone a profound transformation from morphological observation to molecular decoding, as shown in **Figure 1**. Early on, Kerr et al. bifurcated the modes of death into apoptosis and necrosis based on microscopic features. With the discovery of gene regulatory pathways, the concept of programmed cell death (PCD) emerged [7]. Over the last decade, breakthroughs in high-throughput technologies have further revealed metabolism-associated cell death such as ferroptosis and cuproptosis, as well as integrative cell death programs such as PANoptosis [8]. Today's cell death classification system has shifted from a single morphological criterion to multidimensional definitions based on molecular execution mechanisms, regulatory characteristics, and immunological outcomes, as shown in **Table 1**. This section will systematically analyze eight core death modalities, ranging from classic apoptosis and pyroptosis to emerging cuproptosis and PANoptosis, focusing on their molecular switches, morphological hallmarks, and association with inflammation, thereby laying the foundation for understanding the interaction between death and inflammation.

2.1 Apoptosis

Apoptosis is a form of programmed cell death strictly regulated by genes, and is essential for the growth and development, tis-

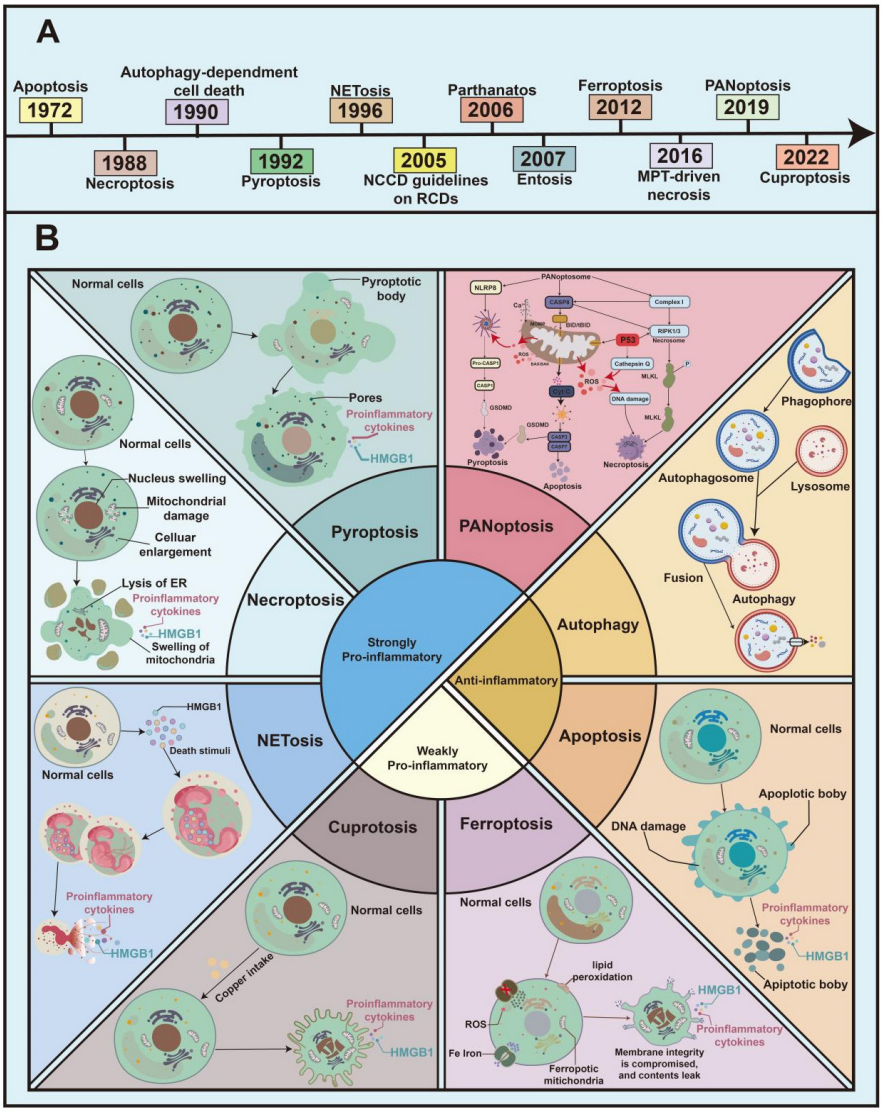

Figure 1. Historical evolution and mechanistic landscape of regulated cell death pathways. (A) Timeline of key discoveries in the field of RCD from 1972 to 2022. Major RCD modalities are annotated with their year of nomenclature or seminal characterization, illustrating the rapid expansion of our understanding beyond apoptosis. (B) A comprehensive schematic diagram categorizing distinct RCD pathways based on their inflammatory potential (ranging from strongly pro-inflammatory to weakly pro-inflammatory or anti-inflammatory) and molecular mechanisms. The central area highlights key pro-inflammatory pathways (necroptosis, pyroptosis, PANoptosis), while the periphery details other modalities. For each pathway, representative cellular and subcellular events are depicted, including morphological changes (e.g., pyknotic nuclei in apoptosis, pore formation in pyroptosis), organelle dynamics (e.g., mitochondrial damage in ferroptosis), and the release of key mediators (e.g., HMGB1, proinflammatory cytokines). This integrative overview emphasizes the connection between specific molecular effectors and the resultant immunological outcomes of different cell death types. RCD, regulated cell death; HMGB1, High Mobility Group Box 1; NETosis, NET formation cell death; NCCD, Nomenclature Committee on Cell Death; MPT, mitochondrial permeability transition; ER, endoplasmic reticulum; NLRP8, NLR family pyrin domain containing 8; CASP8, caspase-8; CASP1, caspase-1; GSDMD, gasdermin D; MOMP, mitochondrial outer membrane permeabilization; BID, BH3-interacting domain death agonist; tBID, truncated BID; ROS, reactive oxygen species; BAX, BCL2-associated X protein; BAK, BCL2-antagonist/killer 1; Cyt C, cytochrome c; CASP3, caspase-3; CASP7, caspase-7; RIPK1/3, receptor-interacting protein kinase 1/3; P53, tumor protein p53; MLKL, mixed lineage kinase domain-like protein.

sue homeostasis, and immune function of multicellular organisms. Unlike necrosis, apoptosis is an active, ordered form of cell suicide [28]. The morphological hallmarks of apoptosis primarily include cell shrinkage, chromatin condensation, and the formation of apoptotic bodies. Apoptotic cells decrease in volume, their cytoskeleton disintegrates, and they detach from surrounding cells. The nucleus undergoes significant changes, with chromatin condensing and aggregating at the nuclear periphery, followed by DNA fragmentation, forming nuclear fragments of varying sizes. The cell membrane blebs to form apoptotic bodies. These bodies, which contain organelles and cytoplasm, are eventually phagocytosed and cleared by neighboring cells or macrophages without eliciting an inflammatory response [29].

Apoptosis is regulated by various factors, including intracellular and extracellular signals, as shown in **Figure 2**. Intracellular signaling pathways primarily involve the mitochondrial pathway, in which BCL-2 family proteins (e.g., Bax, Bak) play a crucial role in regulating mitochondrial membrane permeability. Increased mitochondrial membrane permeability leads to the release of cytochrome c, activating the caspase protease family, and ultimately leading to apoptosis [30]. Extracellular signaling pathways, on the other hand, are mediated by death receptors. For example, Fas ligand binds to the Fas receptor, activating caspase-8, which then initiates downstream apoptotic processes [31]. In addition to the classical apoptotic pathways, there also exist caspase-independent apoptotic pathways. For example, the release of apoptosis-inducing factor and endonuclease G can also lead to chromatin condensation and DNA fragmentation, thereby causing cell death [32].

The mitochondrial (intrinsic) pathway of apoptosis is tightly regulated by BCL-2 family proteins, which are mainly divided into two categories: pro-apoptotic and anti-apoptotic. Pro-apoptotic proteins include Bax and Bak, which, upon receiving apoptotic signals, undergo conformational changes and oligomerization, ultimately leading to mitochondrial outer membrane permeabilization (MOMP) [33]. The occurrence of MOMP is a critical step in the intrinsic apoptotic path-

Table 1. Core molecular characteristics of cell death modalities and their association with inflammation

Cell death modality	Subtype/key pathway	Core molecular executors	Triggering signals	Morphological/ biochemical features	Key regulatory nodes	Inflammatory intensity	Key DAMPs released	References
Apoptosis	Mitochondrial pathway	Cytochrome c, Apaf-1, Caspase-9	DNA damage, ROS	Cell shrinkage, chromatin condensation	Bcl-2/Bax balance	Low	Phosphatidylserine, nucleosomes	[9]
	Death receptor pathway	Caspase-8, FADD	TNF-α, FasL	Membrane blebbing, apoptotic bodies	c-FLIP regulation		/	[10]
	ER stress pathway	Caspase-12, CHOP	ER stress	Cytoplasmic vacuolization	IRE1α-XBP1 axis		ATP	[11]
Pyroptosis	Canonical inflammasome	NLRP3/ASC/ Caspase-1, GSDMD	ATP, K^+ efflux	Cell swelling, GSDMD pore formation	NEK7, ASC oligomerization	High	IL-1β, IL-18, HMGB1	[12]
	Non-canonical pathway	Caspase-4/5/11, GSDMD	Intracellular LPS	Membrane rupture, LDH release	Guanylate-binding proteins		mtDNA	[13]
	Caspase-8-dependent	Caspase-8, GSDMC/E	TNF-α, TLR2/4	Hybrid pyroptotic-apoptotic features	cFLIP regulation		S100A8/9	[14]
Necroptosis	RIPK1-dependent	RIPK1, RIPK3, MLKL	TNF-α (during caspase inhibition)	Membrane permeabilization, cell lysis	RIPK1 ubiquitination status	High	HMGB1, mtDNA	[15]
	RIPK1-independent	ZBP1, RIPK3, MLKL	Viral RNA, IFNs	RIPK3 phosphoaggregation	Zα-domain activation		Heat shock proteins	[16]
Ferroptosis	GPX4-inhibition pathway	GPX4, ACSL4, LPCAT3	Iron overload, Erastin/RSL3	Mitochondrial shrinkage, lipid peroxidation	NRF2-Keap1 axis	Moderate	4-HNE, MDA	[17]
	System Xc^- inhibition	SLC7A11↓, GSH depletion	Cystine deprivation, sorafenib	Lipid ROS accumulation	FSP1 membrane localization		Oxidized phospholipids	[18]
Cuproptosis	Mitochondrial proteotoxicity	FDX1, DLAT, LIAS	Copper ion overload	Mitochondrial protein oligomerization	Copper chaperones (ATOX1)	Moderate	mtDNA, mtROS	[19]
NETosis	Suicidal NETosis	PAD4, MPO, NE	Pathogens, immune complexes	NETs release (chromatin decondensation)	ROS-Ca^{2+} axis	Extreme	Citrullinated histones, LL-37	[20]
	Vital NETosis	/	Cytokine storm	Preserved nuclear envelope	SK3 channel activation		Antimicrobial peptides	[21]
Autophagic cell death	Atg5/7-dependent	Beclin-1, LC3-II	Starvation, rapamycin	Autolysosomal vacuolation	mTOR-ULK1 axis	Low/ Moderate	Low ATP	[22]
	Rab9-dependent alternative	Rab9, UVRAG	Stress-induced	LC3-unlipidated vacuoles	TRAPPIII complex		/	[23]
Alkaliptosis	Na^+/H^+ exchanger dysregulation	NHE1, ASIC1a	Intracellular alkalosis	Cell swelling, vacuolation	Lysosomal pH homeostasis	Low	Cathepsins	[24]
Lysosome-dependent cell death	Cathepsin leakage	Cathepsin B/D, LAMP1	Lysosomal membrane permeabilization	Lysosomal rupture	Galectin-3 surveillance	Moderate	Lysosomal enzymes	[25]
PANoptosis	ZBP1-PANoptosome	ZBP1, RIPK1, Caspase-8	Viral RNA, cytokine storm	Hybrid death features	IRF1 transcriptional regulation	Extreme	Cooperative DAMPs release	[26]
	AIM2-PANoptosome	AIM2, ASC, FADD	Cytosolic DNA	PANoptosome oligomerization	cGAS-STING interaction		/	[27]

Note: DAMPs, damage-associated molecular patterns; Apaf-1, apoptotic protease activating factor 1; ROS, reactive oxygen species; Bcl-2, B-cell lymphoma 2; Bax, BCL2-associated X protein; FADD, Fas-associated death domain protein; TNF-α, tumor necrosis factor-alpha; FasL, Fas ligand; c-FLIP, cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein; ER, endoplasmic reticulum; CHOP, C/EBP homologous protein; IRE1α, inositol-requiring enzyme 1 alpha; XBP1, X-box binding protein 1; ATP, adenosine triphosphate; NLRP3, NLR family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, gasdermin D; NEK7, NIMA-related kinase 7; IL-1β, interleukin-1β; IL-18, interleukin-18; HMGB1, high mobility group box 1; LPS, lipopolysaccharide; LDH, lactate dehydrogenase; mtDNA, mitochondrial DNA; GSDMC, gasdermin C; GSDME, gasdermin E; TLR2, Toll-like receptor 2; TLR4, Toll-like receptor 4; S100A8/9, S100 calcium-binding protein A8/A9; RIPK1, receptor-interacting protein kinase 1; RIPK3, receptor-interacting protein kinase 3; MLKL, mixed lineage kinase domain-like pseudokinase; ZBP1, Z-DNA-binding protein 1; IFNs, interferons; GPX4, glutathione peroxidase 4; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; Erastin/RSL3, ferroptosis inducers (Erastin and RAS-selective lethal 3); NRF2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; System Xc^-, cystine/glutamate antiporter; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; FSP1, ferroptosis suppressor protein 1; FDX1, ferredoxin 1; DLAT, dihydrolipoamide S-acetyltransferase; LIAS, lipoic acid synthetase; ATOX1, antioxidant 1 copper chaperone; mtROS, mitochondrial reactive oxygen species; PAD4, peptidylarginine deiminase 4; MPO, myeloperoxidase; NE, neutrophil elastase; NETs, neutrophil extracellular traps; Ca^{2+}, calcium ion; SK3, small conductance calcium-activated potassium channel 3; LL-37, cathelicidin antimicrobial peptide; Atg5, autophagy-related protein 5; Atg7, autophagy-related protein 7; LC3-II, microtubule-associated protein 1 light chain 3-II; mTOR, mechanistic target of rapamycin; ULK1, UNC-51-like kinase 1; Rab9, Ras-related protein Rab-9; UVRAG, UV radiation resistance-associated gene protein; TRAPPIII, transport protein particle III complex; NHE1, Na^+/H^+ exchanger 1; ASIC1a, acid-sensing ion channel 1a; Cathepsins, lysosomal proteases; LAMP1, lysosomal-associated membrane protein 1; Galectin-3, β-galactoside-binding lectin 3; IRF1, interferon regulatory factor 1; AIM2, absent in melanoma 2; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes.

way, as it leads to the release of cytochrome c from the mitochondrial intermembrane space into the cytoplasm. In the cytoplasm, cytochrome c binds to Apaf-1 and recruits pro-caspase-9 to form the apoptosome [34]. The apoptosome activates caspase-9, and activated caspase-9 subsequently activates downstream effector caspases, such as caspase-3 and caspase-7. These effector caspases are responsible for cleaving various intracellular substrates, ultimately leading to apoptosis [35]. Anti-apoptotic proteins, such as BCL-2 and BCL-xL, inhibit apoptosis by binding to Bax and Bak, preventing their oligomerization and MOMP [36]. BH3 domain proteins (e.g., Bid, Bim, Puma, Noxa, and Bad) initiate apoptosis by binding to anti-apoptotic proteins. Cellular stress and damage activate BH3 proteins, which can bind to anti-apoptotic BCL-2 proteins, enabling Bax and Bak to oligomerize and induce MOMP [37]. The balance between pro-apoptotic and anti-apoptotic proteins determines cell fate. In the extrinsic pathway, cell surface death receptors, such as Fas receptor and TNFR1, initiate apoptotic signals after binding to their respective ligands (FasL and TNF-α) [38]. After FasL binds to the Fas receptor, the Death-Inducing Signaling Complex is formed, which contains FADD and caspase-8. In the complex, caspase-8 is activated, and activated caspase-8 can directly activate downstream caspase-3, initiating the execution of apoptosis. Additionally, caspase-8 can cleave the cytoplasmic Bid protein, producing truncated Bid (tBID). tBID localizes to mitochondria, inducing the release of cytochrome c, thereby cross-linking with the endogenous pathway and amplifying the apoptotic signal [39]. After TNF-α binds to TNFR1, this interaction recruits proteins such as TRADD, FADD, and RIP to form Complex I, activating the NF-κB signaling pathway, leading to anti-apoptotic effects. However, TNFR1 can also indirectly induce apoptosis through FADD-dependent apoptosis and caspase-8, and activated caspase-8 can further activate other apoptotic enzymes such as caspase-3 [35]. Activation of the extrinsic pathway depends on the expression levels and functional status of death receptors, adaptor proteins, and caspases. The two main apoptotic pathways do not operate independently but rather interact with and regulate each other during apoptosis. For example, in the extrinsic pathway, caspase-8 activates Bid, generating tBID, thereby activating the mitochondrial pathway [10]. In the intrinsic pathway, cytochrome c released by mitochondria activates caspase-9, and activated caspase-9 may in turn affect certain components of the death receptor pathway [40]. This crosstalk between pathways ensures the precise regulation and efficient execution of the apoptotic process. Furthermore, BCL-2 family proteins not only regulate the permeability of the mitochondrial outer membrane but also participate in the regulation of endoplasmic reticulum and calcium ion signaling, further influencing cellular apoptotic sensitivity [41, 42].

There is a complex bidirectional relationship between apoptosis and inflammation, where apoptosis can both trigger and inhibit the occurrence of inflammatory responses [43]. Apoptosis is generally considered an immunologically silent mode of cell death that can prevent the occurrence of inflammation. However, in certain circumstances, the apoptotic process itself may trigger inflammatory responses [44]. For example, if apoptotic cells are not promptly cleared, they may undergo secondary necrosis, releasing cellular contents, thereby activating the immune system and inducing inflammation and autoimmune responses. Furthermore, apoptotic cells can also release some endogenous DAMPs, which activate immune cells and promote inflammatory responses [45]. On the other hand, inflammatory responses can also affect the occurrence of apoptosis through multiple pathways. Pro-inflammatory cytokines in the inflammatory environment, such as TNF, can directly induce apoptosis [46]. In addition, substances such as

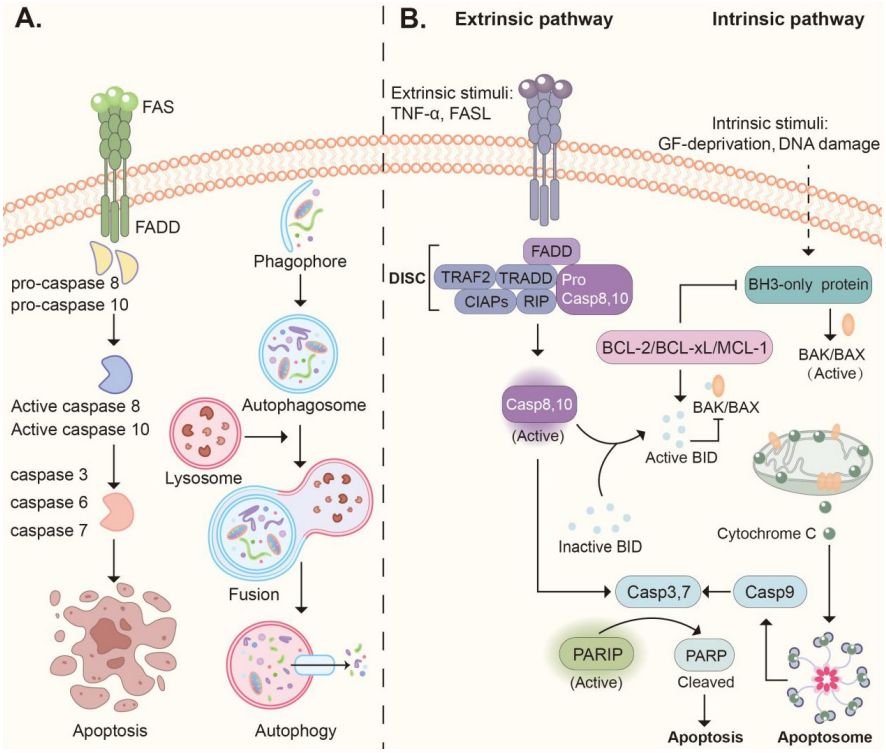

Figure 2. Molecular mechanisms of the extrinsic and intrinsic apoptotic pathways. (A) Schematic overview of a cell, contextualizing the apoptotic signaling cascades within the cellular architecture. (B) Detailed schematic diagram illustrating the key signaling cascades of apoptosis. The extrinsic (death receptor) pathway (left panel) is initiated by the binding of extracellular ligands (e.g., FASL, TNF-α) to their respective death receptors (e.g., FAS). This leads to the formation of the DISC, which recruits and activates initiator Casp8 and Casp10. The intrinsic (mitochondrial) pathway (right panel) is activated by intracellular stresses such as growth factor deprivation or DNA damage, leading to the activation of pro-apoptotic BCL-2 family proteins (e.g., BID, BAX, BAK). This results in MOMP and the release of Cyt C. Cyt C, together with Apaf-1, forms the apoptosome, activating Casp9. Both pathways converge on the activation of executioner Casp3 and Casp7, which cleave cellular substrates like PARP, ultimately leading to apoptotic cell death. Notably, crosstalk between the pathways occurs via Casp8-mediated cleavage of BID to tBID, which amplifies the apoptotic signal through the mitochondrial pathway. FADD, Fas-associated death domain protein; TNF-α, tumor necrosis factor-alpha; FASL, Fas ligand; TRAF2, TNF receptor-associated factor 2; TRADD, TNF receptor-associated death domain protein; CIAPs, cellular inhibitors of apoptosis proteins; RIP, receptor-interacting protein; Casp8, caspase-8; Casp9, caspase-9; Casp10, caspase-10; BID, BH3-interacting domain death agonist; BAK, BCL2-antagonist/killer 1; BAX, BCL2-associated X protein; Casp3, caspase-3; Casp7, caspase-7; PARP, poly(ADP-ribose) polymerase; Apaf-1, apoptotic protease activating factor 1; tBID, truncated BID; MOMP, mitochondrial outer membrane permeabilization; Cyt C, cytochrome c; FAS, Fas cell surface death receptor; DISC, Death-Inducing Signaling Complex; GF-deprivation, growth factor deprivation; BCL-2, B-cell lymphoma 2; BCL-xL, B-cell lymphoma-extra large; MCL-1, Myeloid cell leukemia 1; PARP, Poly(ADP-ribose) polymerase.

reactive oxygen species (ROS) and reactive nitrogen species produced during the inflammatory response may also damage cells and promote the occurrence of apoptosis [47]. Therefore, apoptosis and inflammation mutually influence each other, jointly participating in maintaining body homeostasis. The occurrence of inflammation is closely related to the life cycle of immune cells. Apoptosis, as a form of programmed cell death, plays an important role in the process of inflammation resolution. By promoting the apoptosis of inflammatory cells such as neutrophils, the intensity and duration of the inflammatory response can be effectively controlled [48]. Studies have shown that the pro-apoptotic protein ARTS can induce neutrophil apoptosis, promote the clearance of apoptotic cells, and remodel macrophage function, thereby promoting inflammation resolution [49]. During the clearance of apoptotic cells, macrophages release anti-inflammatory factors, further inhibiting the inflammatory response [50]. Zinc has antioxidant, anti-inflammatory, and cell death-regulating effects [51]. It can inhibit the activity of caspase-3, -7, and -8, thereby regulating caspase-dependent apoptosis and necroptosis. In diseases such as COVID-19 and sepsis, the immunomodulatory role of zinc has received widespread attention.

2.2 Pyroptosis

Pyroptosis, as an inflammatory form of programmed cell death, has a core molecular execution mechanism that primarily relies on the activation of Gasdermin family proteins, particularly GSDMD, and its process of forming pores on the cell membrane [52]. Pyroptosis not only plays a role in anti-infection immunity, protecting the body by clearing intracellular pathogens and damaged cells, but also plays an important role in tumor immunity, influencing the occurrence, development, and treatment of tumors. However, uncontrolled pyroptosis can lead to excessive inflammatory activation and tissue damage, and is closely related to the occurrence and development of various diseases, including cardiovascular diseases, neurological diseases, and autoimmune diseases [53]. Therefore, in-depth research into the molecular mechanisms and biological functions of pyroptosis helps to develop therapeutic strategies for related diseases.

The initiation of the classical pyroptosis pathway depends on the activation of intracellular inflammasomes, as shown in **Figure 3**. Inflammasomes are a type of multiprotein complex that recognizes pathogen-associated molecular patterns (PAMPs) and DAMPs. Common inflammasomes include NLRP3, NLRC4, NLRP1b, and AIM2, among others [54].

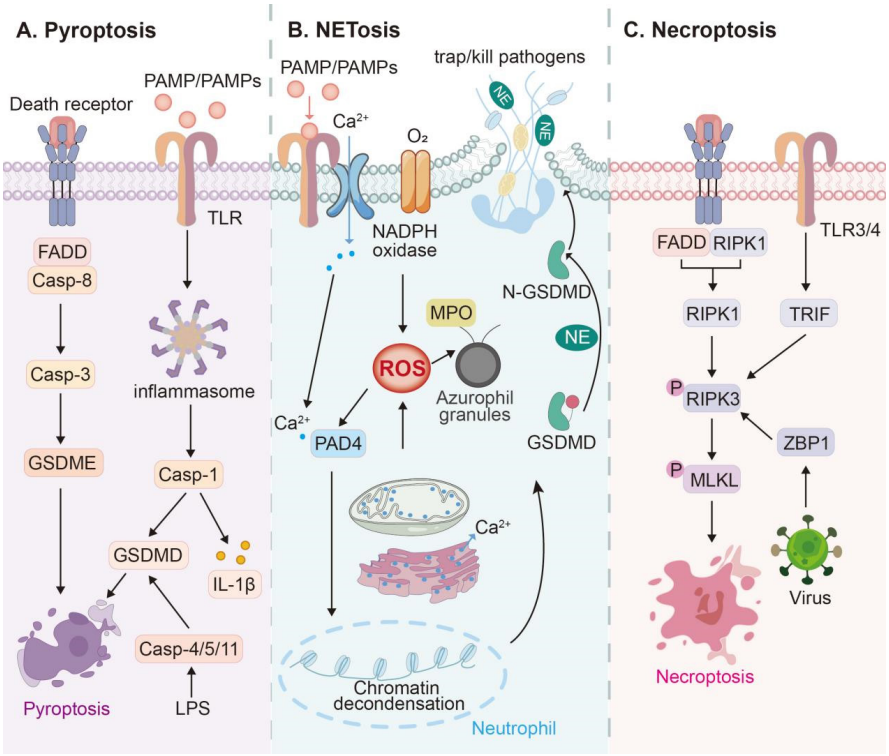

Figure 3. Molecular mechanisms of key pro-inflammatory cell death pathways: pyroptosis, NETosis, and necroptosis. Schematic models depicting the signaling cascades of three distinct pro-inflammatory regulated cell death pathways. (A) Pyroptosis. Activation by PAMPs or DAMPs through TLRs or death receptors recruits adaptor proteins (e.g., FADD) and activates inflammatory caspases (Casp-1/4/5/11) or, in certain contexts, Casp-8. These caspases cleave GSDMD or GSDME, liberating the N-GSDMD that oligomerizes and forms pores in the plasma membrane. This leads to osmotic lysis (pyroptosis) and the release of mature IL-1β. (B) NETosis. In neutrophils, PAMPs trigger Ca^{2+} influx and activate NADPH oxidase to generate ROS. ROS promote PAD4-mediated histone citrullination and chromatin decondensation. NE and MPO translocate to the nucleus, and together with GSDMD (which may facilitate the process), lead to the expulsion of NETs composed of DNA and granular proteins to trap pathogens. (C) Necroptosis. When triggered by viral infection or TNF signaling, necroptosis involves the inhibition of Casp-8 activity, which allows the activation of RIPK1 and RIPK3. RIPK3 phosphorylates MLKL, which oligomerizes, translocates to, and disrupts the plasma membrane, resulting in necroptotic cell death. These pathways represent crucial mechanisms by which the innate immune system eliminates infected or damaged cells while amplifying inflammatory responses. PAMP, pathogen-associated molecular pattern; TLR, Toll-like receptor; FADD, Fas-associated death domain protein; Casp-1, caspase-1; Casp-8, caspase-8; Casp-3, caspase-3; GSDME, gasdermin E; GSDMD, gasdermin D; IL-1β, interleukin-1β; Casp-4/5/11, caspase-4/5/11; LPS, lipopolysaccharide; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; ROS, reactive oxygen species; PAD4, peptidylarginine deiminase 4; N-GSDMD, N-terminal fragment of gasdermin D; MPO, myeloperoxidase; TRIF, TIR-domain-containing adapter-inducing interferon-β; ZBP1, Z-DNA-binding protein 1; MLKL, mixed lineage kinase domain-like pseudokinase; RIPK1, receptor-interacting protein kinase 1; RIPK3, receptor-interacting protein kinase 3; NE, neutrophil elastase; TLR3/4, Toll-like receptor 3/4; DAMP, damage-associated molecular pattern; NET, neutrophil extracellular trap.

Upon activation, they recruit ASC and pro-caspase-1 to form an inflammasome complex. Within the complex, pro-caspase-1 is activated into caspase-1, which is capable of cleaving pro-IL-1β and pro-IL-18, converting them into mature IL-1β and IL-18. Simultaneously, caspase-1 also cleaves GSDMD, releasing its N-terminal domain (GSDMD-N) [55]. After oligomerization, GSDMD-N inserts into the cell membrane, forming pores, an event that leads to an imbalance of ion concentrations inside and outside the cell, cell swelling and rupture, and the release of cellular contents, including pro-inflammatory cytokines such as IL-1β and IL-18. The release of these cytokines further exacerbates the inflammatory response [56, 57]. The non-canonical pyroptosis pathway does not depend on caspase-1, but is activated through caspase-4/5/11 (caspase-11 in mice). These caspases can directly recognize intracellular LPS, thereby activating GSDMD [58]. Activated GSDMD-N also forms pores on the cell membrane, leading to pyroptosis and the release of inflammatory mediators. In addition to the classical and non-classical pathways, some other pathways are also involved in the regulation of pyroptosis. For example, caspase-8 can be activated through the TLR2/4 or TNFR signaling pathways, subsequently activating GSDMC/E. The expression of GSDME is suppressed in many tumor cells, but when its expression is restored, the activation of caspase-3 can lead to GSDME-mediated pyroptosis, thereby inhibiting tumor growth [10, 59]. Furthermore, mechanical force activates TRPV4, leading to calcium ion influx and stimulating the production of ROS, which can also ultimately lead to pyroptosis [60]. In-depth study of these pathways helps us better understand the essence of inflammatory responses and cell death, and provides new insights and strategies for the treatment of related diseases.

A significant context in which pyroptosis plays a critical pathogenic role is acute lung injury (ALI) during the perioperative period. Here, alveolar epithelial cell pyroptosis, driven by NLRP3 inflammasome activation, is a key mechanism amplifying injury. Surgical trauma, mechanical ventilation, hypoxia, or infections can provide both priming (e.g., via NF-κB upregulation of NLRP3 and pro-IL-1β) and activation signals (e.g., via K^+ efflux, ROS, or DAMPs) for the NLRP3 inflammasome [61]. Its assembly activates caspase-1, which cleaves GSDMD to cause pyroptotic pore formation, and processes pro-IL-1β into its mature, releasable form. This results in alveolar barrier disruption, edema, and a

potent local and systemic inflammatory cascade. Preclinical models, such as ventilator-induced lung injury, have been instrumental in delineating this pathway. Mechanical stress can activate NLRP3, and inhibition of this pathway (e.g., via FGF21 or ASK1 deficiency) attenuates ventilator-induced lung injury [62, 63]. Furthermore, in sepsis-induced ALI or one-lung ventilation settings, modulating the NLRP3/GSDMD axis (e.g., with sevoflurane, melatonin, or Rebastinib) shows protective effects, highlighting its potential as a therapeutic target to mitigate postoperative ALI [64-66].

Pyroptosis is an inflammatory form of cell death that amplifies inflammatory responses through multiple pathways and plays a crucial role in the pathophysiological processes of various diseases. Pyroptosis not only directly leads to the release of cellular contents but also indirectly amplifies inflammatory signals by activating multiple inflammatory pathways and immune cells, forming a complex inflammatory amplification network. After pyroptotic cells rupture, a large number of pro-inflammatory factors, such as IL-1β and IL-18, are released, which can significantly activate adjacent immune cells and tissue cells, further amplifying the inflammatory response [67, 68]. Among these, IL-1β is particularly crucial, as it can induce various cells to produce more inflammatory mediators (such as TNF-α and IL-6), forming an inflammatory cascade [69]. Secondly, the cellular contents and pro-inflammatory factors released by pyroptosis can strongly attract and activate immune cells such as neutrophils, macrophages, and T cells. These immune cells recruited to the inflammatory site will release more inflammatory mediators and ROS, exacerbating local tissue damage [70]. In addition, the pyroptosis-mediated inflammatory response profoundly affects the composition and structure of the extracellular matrix (ECM). For example, the upregulation of the ECM component Versican by cytokines in the early stage of inflammation promotes the progression of the inflammatory response [71]. At the same time, pyroptosis is closely linked to immunometabolism. Inflammatory signals can alter cellular metabolic pathways, while the metabolic state of immune cells (e.g., ATP metabolism) directly affects inflammasome activation and inflammatory factor release [72, 73]. For example, B cell-derived extracellular vesicles can affect $CD8^+$ T cell responses by hydrolyzing ATP. Under specific pathological conditions, such as systemic lupus erythematosus (SLE), autoantibodies (e.g., anti-dsDNA antibodies) can also amplify pyroptosis-related inflammatory responses.

This potent inflammatory amplification effect enables pyroptosis to play important roles in both host immune defense and disease development. Pyroptosis is a crucial mechanism for the host to combat pathogen infection. When pyroptosis is induced in infected cells, intracellular pathogens can be cleared, and inflammatory factors are released, activating immune cells and enhancing host immune responses [74]. In sepsis, although pyroptosis acts as a host defense mechanism to clear pathogens, the inflammatory storm caused by its overactivation can significantly worsen the condition [75]. Pyroptosis plays a complex role in tumor initiation and progression. On the one hand, pyroptosis can inhibit tumor initiation. Inducing pyroptosis in tumor cells can directly kill them, release tumor-associated antigens, and activate anti-tumor immune responses [76]. On the other hand, studies have shown that pyroptosis may also promote tumor metastasis and drug resistance [77]. Inflammatory factors released by pyroptosis can promote the formation of the tumor microenvironment and inhibit the activity of anti-tumor immune cells. Therefore, a deeper understanding of the regulatory mechanisms of pyroptosis and its role in diseases helps develop new therapeutic strategies to control inflammatory responses and improve disease prognosis. For example, regulating the ubiquitination level of the NLRP3 inflammasome can modulate the intensity of inflammatory responses [78]. Additionally, some natural compounds, such as DIM, can alleviate inflammatory responses by regulating the AhR/NF-κB signaling pathway [79]. Drugs targeting GSDMD and MLKL also hold promise as new therapeutic approaches for inflammation-related diseases [80]. Future research should focus on elucidating the interactions between pyroptosis and other forms of cell death (such as apoptosis, necroptosis, and ferroptosis), as well as developing more precise therapeutic approaches targeting pyroptosis.

2.3 Necrosis

Necrosis is a form of cell death previously considered a non-programmed, accidental event. However, it is now known that necrosis can also occur through regulated pathways, referred to as regulated necrosis, such as necroptosis [81]. Therefore, currently, cell death is broadly classified into accidental necrosis and PCD, with necroptosis being a subtype of PCD rather than a category parallel to accidental necrosis. In this framework, necrosis, in a broad sense, includes two forms. One is accidental necrosis in the traditional sense, which is uncontrollable; the other is regulated necroptosis. Necrosis differs from apoptosis, in that apoptosis is a form of programmed cell death that does not induce an inflammatory response, whereas necrosis is usually associated with inflammation. Accidental necrosis is usually caused by external factors, such as physical injury, chemical substances, or ischemia [82]. These factors lead to the loss of cell membrane integrity, resulting in the uncontrolled release of cellular contents into the extracellular environment. These released cellular contents, including DAMPs, can activate immune cells, leading to inflammatory responses [83]. In contrast, regulated necrotic pathways such as necroptosis represent programmed cell death pathways that can also lead to inflammation in some cases. Unlike accidental necrosis, these regulated pathways are triggered by specific molecular signaling pathways. TNF is one of the most extensively studied triggers of necroptosis [84]. When cells fail to initiate apoptosis, TNF binds to its receptor, activating RIPK1. RIPK1 recruits and activates RIPK3, forming a complex known as the necrosome. RIPK3 phosphorylates MLKL, leading to MLKL oligomeriza-

tion and translocation to the plasma membrane. MLKL oligomerization in the plasma membrane results in membrane rupture and the release of cellular contents, thereby leading to inflammation [85].

Inflammation is a key outcome of both accidental necrosis and regulated necrotic pathways, but the two modes of cell death trigger inflammation through different mechanisms. In accidental necrosis, inflammation is primarily caused by the non-specific release of cellular contents. DAMPs, such as heat shock proteins and HMGB1, can bind to PRRs on immune cells, such as Toll-like receptors (TLRs), thereby activating inflammatory pathways [83]. In regulated necrotic pathways, inflammation is driven by specific molecular mediators released in a controlled manner. For example, MLKL-mediated plasma membrane rupture leads to the release of cytokines such as IL-1β and IL-18, which are potent inflammatory inducers [86]. Furthermore, regulated necrotic pathways can promote inflammation by activating inflammasomes, which are multiprotein complexes in the cytoplasm that activate caspase-1 and lead to the maturation of IL-1β and IL-18 [87]. There are multiple types of programmed cell death, including necroptosis, pyroptosis, and ferroptosis, which lead to inflammation through different molecular mechanisms [88, 89]. Necroptosis is primarily mediated by RIPK1, RIPK3, and MLKL. When caspases are inhibited, RIPK1 and RIPK3 form a necrosome, leading to MLKL phosphorylation and translocation to the plasma membrane, ultimately resulting in membrane rupture and the release of inflammatory mediators. Pyroptosis, on the other hand, is mediated by the gasdermin protein family. Inflammasomes activate caspase-1, which cleaves GSDMD. The GSDMD-N fragment forms pores in the plasma membrane, releasing cellular contents and inflammatory factors. Ferroptosis is a form of cell death driven by iron-dependent lipid peroxidation, leading to the production of ROS and the release of lipid peroxidation products, which can activate immune cells and promote inflammation. Overall, accidental necrosis primarily triggers inflammation through the non-specific release of cellular contents, while regulated necrotic pathways release cellular contents and inflammatory mediators in an orderly manner through the activation of regulatory proteins and the transmission of signaling pathways, thereby initiating a more precise immune response.

Regulated necrotic pathways, as forms of programmed cell death, play a complex and crucial role in the initiation and progression of various diseases. They are characterized by the rupture of the cell membrane and the release of cellular contents, events that trigger inflammatory responses and immune activation. These cell death pathways are associated with various pathological processes, including but not limited to infectious diseases, neurodegenerative diseases, cancer, and cardiovascular diseases [90]. In infectious diseases, regulated necrotic pathways can serve as a defense mechanism by inducing the death of infected cells to limit the spread of pathogens and activate the immune system to clear pathogens [91]. However, regulated necrotic death may also lead to excessive inflammatory responses and tissue damage, exacerbating the severity of the disease. In neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, regulated necrotic pathways are believed to be involved in the death of neurons, thereby leading to cognitive dysfunction and motor disorders [92, 93]. In cardiovascular diseases, such as myocardial infarction, regulated necrotic pathways may lead to the death of cardiomyocytes and impaired myocardial function [94]. In the tumor microenvironment, regulated necrotic pathways can act as a pro-tumor mechanism, promoting tumor growth and metastasis through inflammation, or as an anti-tumor mechanism. For example, they can be harnessed by integrating natural compounds such as polyphenols, alkaloids, and terpenes to induce tumor cell death, thereby inhibiting tumor progression [95-97]. Intervention strategies targeting regulated necrotic pathways have become a research hotspot. Recent studies have shown that targeting necroptosis can induce anti-tumor immunity, which is crucial for improving cancer treatment [98]. Immunogenic cell death (ICD) can eliminate residual cancer cells by activating the immune system, and necroptosis is a form of ICD. Therefore, therapeutic strategies targeting necroptosis can enhance anti-tumor immune responses and improve therapeutic efficacy. Meanwhile, RIPK3 plays a role in the crosstalk between cell death and inflammation, interacting with RIPK1 to form a necrosome, thereby triggering caspase-independent programmed necrosis [91]. RIPK3 is involved in various infections, aseptic inflammatory diseases, and the pathological processes of tumors, and thus has also become a potential therapeutic target.

A particularly relevant example of the detrimental effects of excessive necroptosis is its contribution to intestinal barrier dysfunction and postoperative infection susceptibility. The intestinal epithelial barrier, maintained by a monolayer of enterocytes and tight junctions, is critical for preventing bacterial and toxin translocation. Perioperative stressors such as surgical trauma, gut ischemia-reperfusion injury, or sepsis can trigger RIPK1/RIPK3/MLKL-mediated necroptosis in enterocytes [99, 100]. Central to this process is the oligomerization of phosphorylated MLKL, which forms pores in the plasma membrane, leading to the lysis of enterocytes. This "lytic" cell death directly disrupts the physical continuity of the epithelial layer, compromising tight junction function and increasing intestinal permeability [101]. The resulting barrier failure allows gut-derived bacteria and PAMPs (e.g., LPS) to enter the systemic circulation, potentially initiating or amplifying systemic inflammatory response syndrome (SIRS) and sepsis. In conditions like necrotizing enterocolitis and inflammatory bowel disease (IBD), upregulated RIPK3/MLKL expression and enterocyte necroptosis are observed. Conversely, inhibiting this pathway (e.g., via RIPK1 inhibitors or compounds like curcumin) alleviates intestinal damage in models. Thus, targeting necroptosis emerges as a promising strategy to preserve intes-

tinal barrier integrity and reduce the risk of postoperative, gut-originated infections [102].

2.4 Ferroptosis

Ferroptosis is a form of cell death driven by iron-dependent lipid peroxidation, distinct from other forms of cell death, as it does not rely on caspase activation and membrane pore formation [103, 104]. The core molecular mechanism of ferroptosis is regulated through two pathways. Among them, the GPX4-dependent pathway plays a central role. GPX4 utilizes glutathione (GSH) as a coenzyme and is responsible for reducing intracellular lipid peroxides to maintain redox balance [105]. When GPX4 activity is directly inhibited (e.g., by the action of RSL3, sorafenib) or when GSH supply is insufficient, lipid peroxides cannot be effectively cleared, leading to their accumulation and driving ferroptosis [106]. GSH synthesis depends on cystine uptake, which is mediated by the cystine/glutamate antiporter system Xc^- (composed of SLC7A11 and SLC3A2) [107]. Compounds such as Erastin inhibit system Xc^-, reduce cystine uptake, thereby inhibit GSH synthesis, and indirectly affect GPX4 function. Another important pathway involves dysregulation of iron metabolism [108]. Intracellular iron exists in two forms: Fe^{2+} and Fe^{3+}. Transferrin binds Fe^{3+}, and this complex enters cells via TFR1. After entering the cell, iron can be stored in ferritin. Intracellular iron ions (especially Fe^{2+}) generate a large amount of ROS through the Fenton reaction, directly driving lipid peroxidation [109]. Notably, autophagic degradation of ferritin (ferritinophagy) releases iron ions, exacerbating ferroptosis [110]. Furthermore, several key metabolic regulatory hubs are crucial for the occurrence of ferroptosis. System Xc^-, serving as a gateway for cystine uptake, directly affects downstream GSH synthesis and GPX4 activity through its functional status [109]. ACSL4 functions at the level of lipid metabolism. It converts arachidonic acid (AA) into AA-CoA, which then participates in the formation of phosphatidylethanolamine-AA, thereby providing substrates for lipoxygenases (ALOXs) to catalyze lipid peroxidation [111]. ALOXs directly catalyze the oxidation of these phospholipids, generating lipid hydroperoxides, ultimately leading to cell membrane damage and ferroptosis. Therefore, system Xc^-, ACSL4, and ALOXs collectively constitute key metabolic nodes that regulate ferroptosis sensitivity.

Ferroptosis, as a form of cell death driven by iron-dependent lipid peroxidation, has complex interactions with inflammatory responses. During ferroptosis, lipid peroxidation generates abundant lipid peroxidation products, such as 4-HNE and MDA [112]. These substances, acting as DAMPs, can activate the TLR4/NF-κB pathway. When TLR4 is activated by DAMPs, it initiates the NF-κB signaling pathway, leading to increased expression and secretion of downstream inflammatory factors, such as IL-6 and TNF-α [113]. These inflammatory factors further exacerbate inflammatory responses and affect the function of the immune system. In addition, mitochondrial damage is also an important factor in ferroptosis-triggered inflammation. During ferroptosis, mitochondrial function is impaired, leading to mtDNA leakage into the cytoplasm. Cytoplasmic mtDNA is recognized by cyclic GMP-AMP synthase (cGAS), activating the cGAS-STING pathway [114]. Upon STING activation, this pathway promotes the release of type I interferons, further enhancing the inflammatory response. In cancer, STING activation can promote anti-tumor immunity by enhancing antigen presentation, recruiting immune cells, and inhibiting metastasis.

A significant disease context linking ferroptosis to inflammation and cellular damage is POCD, which is particularly relevant in elderly patients. Surgical stress and anesthesia can trigger central nervous system inflammation and oxidative stress, especially in the hippocampus, leading to impaired GPX4 function and subsequent neuronal ferroptosis [115]. In POCD animal models, decreased GPX4 expression/activity, along with elevated lipid peroxidation markers (e.g., MDA), iron accumulation, and GSH depletion, is commonly observed [116]. This GPX4 dysfunction-driven ferroptosis not only causes direct neuronal damage but also interacts with neuroinflammation and calcium dyshomeostasis, forming a vicious cycle that accelerates cognitive decline. For instance, GPX4 inhibition can enhance ryanodine receptor-mediated calcium release, further promoting ferroptosis, while damage-associated molecules released during ferroptosis exacerbate neuroinflammation. Conversely, overexpression of GPX4 or its transcriptional regulator MEF2C can suppress hippocampal ferroptosis, alleviate neuroinflammation, and improve cognitive performance in models [117]. Consequently, targeting the GPX4-ferroptosis axis is a promising strategy for POCD intervention. Approaches such as using electroacupuncture, which may modulate iron metabolism proteins like TFR1, DMT1, and FPN, as well as supplying GPX4 substrates (e.g., N-acetylcysteine), using iron chelators or lipophilic radical-trapping antioxidants, and applying neuroprotective near-infrared light, have shown anti-ferroptotic and cognitive protective effects in preclinical studies [118]. Furthermore, regulating mitochondrial calcium homeostasis (e.g., via MICU1 overexpression) or inhibiting ferritinophagy may also influence neuronal ferroptosis sensitivity [119].

Given the critical role of ferroptosis in the pathological processes of various diseases, researchers are actively developing targeted intervention strategies, which have shown potential in preclinical studies. In the field of neurodegenerative diseases, such as Parkinson's disease, ferroptosis has been confirmed to be involved in the damage process of dopaminergic neurons [120]. The application of GPX4 agonists such as Liproxstatin-1 can effectively reduce the accumulation of lipid peroxides within neurons, thereby inhibiting ferroptosis and providing a potential pathway to delay the progression of such diseases. For myocardial ischemia-reperfusion injury, ferroptosis similarly exacerbates the death of cardiomyocytes [121]. In this context,

the use of iron chelators (such as deferoxamine) to reduce intracellular unstable iron ion levels and inhibit free radical generation has become an effective strategy for mitigating myocardial ferroptosis and tissue damage. Furthermore, regulating the expression or activity of key ferroptosis pathway proteins such as ACSL4 and GPX4 has also been proven to protect cardiac function [122, 123]. In tumor therapy, inducing cancer cells to undergo ferroptosis has shown unique value. Studies have found that promoting ferroptosis in tumor cells can significantly enhance the efficacy of immunotherapy, for example, by increasing the sensitivity of tumors to immune checkpoint inhibitors such as PD-1 antibodies [124]. Therefore, the combined application of ferroptosis inducers and immune checkpoint inhibitors, aiming to enhance the body's anti-tumor immune response through a dual mechanism, is considered a synergistic anti-tumor strategy with broad prospects.

2.5 Cuproptosis

Cuproptosis is a programmed cell death first reported by Tsvetkov's team in *Science* in 2022. It is triggered by excessive copper ions (Cu^{2+}) and specifically targets the mitochondrial respiratory chain. Its key molecular mechanism involves the binding of copper to lipoylated tricarboxylic acid cycle enzymes, leading to protein aggregation and cell death [125]. Cuproptosis causes proteotoxic stress and reduces iron-sulfur cluster proteins through copper-dependent abnormal oligomerization reactions, a process that distinguishes it from other forms of cell death. When copper ion concentration exceeds the physiological threshold, excessive copper ions specifically bind to FDX1 and its downstream proteins in the mitochondrial respiratory chain. This binding leads to the loss of function of the key metabolic enzyme DLAT and promotes the oligomerization of these target proteins [126]. Oligomerized proteins further form insoluble aggregates intracellularly (especially in mitochondria), triggering severe proteotoxic stress. Ultimately, this series of events disrupts normal mitochondrial function, particularly interfering with the tricarboxylic acid cycle and respiratory chain electron transport processes, leading to cellular energy metabolism collapse and irreversible death.

Cuproptosis is closely related to mitochondrial metabolism, and copper ion overload can lead to the release of mitochondrial components, which include DAMPs and cytokines [127]. DAMPs and cytokines can activate immune cells, leading to sterile inflammation, which in turn causes tissue damage and remodeling. Furthermore, copper ions can participate in redox reactions, leading to the production of ROS, thereby triggering oxidative stress [128]. Oxidative stress is a state of intracellular imbalance between oxidants and antioxidants, where excessive oxidants can cause damage to cells and activate inflammatory responses. This is similar to the mechanism of ferroptosis-induced inflammation. Meanwhile, both ferroptosis and cuproptosis play significant roles in tumor cell proliferation, metastasis, and drug resistance [129, 130]. Ferroptosis is associated with chemoresistance, and inducing ferroptosis may be a method to address chemoresistance. Furthermore, cuproptosis exhibits a chemosensitizing effect in cancer and can overcome chemoresistance. For example, copper ionophores can be used in combination with chemotherapeutic drugs to increase the intracellular copper ion concentration in cancer cells, thereby inducing cuproptosis and enhancing chemosensitivity [131]. Meanwhile, studies have shown that some cancer cells that develop resistance to traditional chemotherapy drugs are still sensitive to cuproptosis [132]. This makes cuproptosis-based cancer therapy a new research focus. Furthermore, cuproptosis can be used in combination with other cancer treatment modalities to achieve better therapeutic effects. For example, cuproptosis can be combined with immunotherapy to enhance tumor immunogenicity and improve the efficacy of immunotherapy [133]. However, copper ions can promote PD-L1 expression and tumor immune evasion, giving cuproptosis a dual nature in immunotherapy. In the future, the use of copper chelators to target and regulate intracellular copper ion homeostasis in tumor cells is expected to provide new ideas and methods for tumor immunotherapy.

2.6 Autophagy

Autophagy is a lysosome-mediated degradation process of cytoplasmic components, playing a dual role in cell fate. Under basal conditions, autophagy acts as a cell protective mechanism by clearing damaged organelles, misfolded proteins, and invading pathogens to maintain cellular homeostasis [134]. However, under specific conditions, such as sustained stress stimuli or regulatory imbalance, autophagy may be excessively activated, leading to autophagy-dependent cell death, also known as autophagic cell death [135]. The molecular pathway of autophagic cell death differs from traditional apoptosis and necrosis, and its morphological features include cytoplasmic vacuolization and nuclear condensation [136]. Autophagy's dual functions depend on the precise regulation of its core molecules, such as Beclin1 and ATG family proteins [31]. The transition of autophagy from a protective mechanism to a death-promoting function is influenced by various factors, including excessive stress and the activation of specific molecular switches, while the dependence on ATG5/ATG7 determines the occurrence of autophagic cell death.

The molecular regulatory mechanism of autophagy is complex and intricate, involving multiple key proteins and protein complexes, among which the ULK1 complex and PI3K complex play a central role in the autophagy initiation phase [137]. The ULK1 complex is composed of ULK1, ATG13, FIP200, and ATG101, and the activation of this complex is regulated by AMPK and mTOR [138]. Under nutrient-rich conditions, mTORC1 inhibits the ULK1 complex, thereby inhibiting autophagy [139]. Conversely, under conditions of nutrient deprivation or cellular stress, AMPK is activated and phosphorylates the ULK1 complex, thereby initiating autophagy

[140]. The PI3K complex, comprising Beclin1, Vps34, ATG14, and Vps15, is responsible for generating PI3P, which is crucial for phagophore formation [141]. During autophagosome formation, two ubiquitin-like conjugation systems play crucial roles [142]. Firstly, the formation of the ATG12-ATG5-ATG16L1 complex promotes the lipidation of LC3. LC3 is microtubule-associated protein 1 light chain 3, and its lipidated form, LC3-II, binds to the autophagosomal membrane, facilitating autophagosome formation. Although LC3 lipidation is widely used as an indicator of autophagy, it is absent in ATG5/ATG7-independent alternative autophagy [143]. This alternative pathway forms autophagosomes through the fusion of Rab9-mediated phagophores with trans-Golgi network/late endosome-derived vesicles [144]. This reveals that mammalian autophagy exists in two main forms: the classical ATG5/ATG7-dependent pathway and the alternative Rab9-dependent pathway. The fusion of autophagosomes with lysosomes is the final stage of the autophagic process. This fusion event is mediated by SNARE proteins, forming autolysosomes [145]. Inside the autolysosomes, lysosomal enzymes degrade the sequestered cellular material and release degradation products such as amino acids, fatty acids, and nucleotides back into the cytoplasm for cellular reuse.

There are complex interactions between autophagy and other forms of cell death such as apoptosis and necrosis. Autophagy can affect the occurrence of apoptosis through multiple pathways. For example, autophagy can clear mitochondria, thereby inhibiting mitochondria-mediated apoptosis [31]. In addition, autophagy can degrade apoptosis-related proteins such as caspase, thereby inhibiting the occurrence of apoptosis. However, in gastric cancer, autophagy can also promote apoptosis [146]. Cleavage of Beclin1 is considered an important molecular switch for the autophagy-to-death transition. Caspase-8 can cleave Beclin1, thereby inhibiting the protective function of autophagy and potentially promoting apoptosis [147]. Furthermore, cleavage of Beclin1 may release pro-apoptotic factors, such as Bax, further promoting cell death. The relationship between autophagy and necrosis is also highly complex. Necrosis is a form of non-programmed cell death, usually resulting from severe physical or chemical damage to cells. Autophagy can inhibit the occurrence of necrosis by clearing damaged organelles and protein aggregates [148]. However, autophagy can also lead to cellular energy depletion by degrading energy substances such as ATP, ultimately resulting in the occurrence of necrosis [149].

Autophagy plays a complex bidirectional regulatory role in the inflammatory response. On the one hand, autophagy can inhibit inflammation by clearing intracellular damaged substances and pathogens. It can also degrade damaged mitochondria and reduce the production of ROS, thereby alleviating oxidative stress and inflammatory responses [150]. In addition, autophagy can clear misfolded proteins and aggregates, preventing them from triggering inflammatory responses. On the other hand, autophagy can also enhance inflammatory signals by selectively degrading certain anti-inflammatory molecules [151]. It is also involved in the activation of inflammasomes, promoting the release of inflammatory factors. Due to the complexity of autophagy in inflammatory responses, it plays a dichotomous role in various diseases, having both protective and pathogenic effects. In Alzheimer's disease, autophagy can promote the clearance of β-amyloid protein, but overactivated autophagy may also lead to neuronal damage [152]. In IBD, autophagy plays an important role in maintaining intestinal homeostasis and regulating gut microbiota. Autophagy of intestinal macrophages can clear pathogens and damaged cells in the intestine, reducing inflammatory responses [153]. Studies have found that, in Crohn's disease, mutations in the ATG16L1 gene lead to autophagy dysfunction, increasing the risk of intestinal inflammation [154]. However, autophagy may promote macrophage M1 polarization, and M1 macrophages primarily produce pro-inflammatory factors, exacerbating the inflammatory response [155]. Given the complex role autophagy plays in inflammation and disease, therapeutic strategies targeting autophagy require careful consideration. Currently, there are many drugs and natural compounds that can modulate autophagy activity. For example, Rapamycin is an mTOR inhibitor that can enhance autophagy [156]. Flavonoids, such as quercetin, can promote autophagy by activating the AMPK pathway [157]. Furthermore, traditional Chinese medicine has shown potential in modulating autophagy and inflammation. Traditional Chinese medicine, especially Fangji Huangqi Decoction, has been used to treat rheumatoid arthritis (RA) [158]. Future research needs to further elucidate the specific mechanisms of autophagy in different diseases, providing a theoretical basis for developing more effective therapeutic strategies.

2.7 Other types of cell death

NETosis and PANoptosis are both important cell death modalities in inflammatory responses, but they exhibit significant differences in mechanisms and functions. NETosis is primarily executed by neutrophils to capture and kill pathogens, but excessive activation can lead to inflammation and tissue damage [159]. PANoptosis, however, is a more complex cell death modality, integrating multiple pathways of apoptosis, pyroptosis, and necroptosis, playing important roles in both immune defense and inflammatory responses. NETosis is a neutrophil-specific programmed cell death. This process involves the release of web-like structures by neutrophils. These structures, known as neutrophil extracellular traps (NETs), contain DNA, histones, and granular proteins [160]. The primary function of NETs is to trap and kill pathogens, thereby limiting the spread of infection. However, excessive NETosis can lead to the accumulation of NETs in tissues, inducing inflammatory responses, and it is associated with various diseases, including autoimmune diseases, thrombosis, and organ damage [161]. On the other hand, PANoptosis is a newly discovered inflammatory

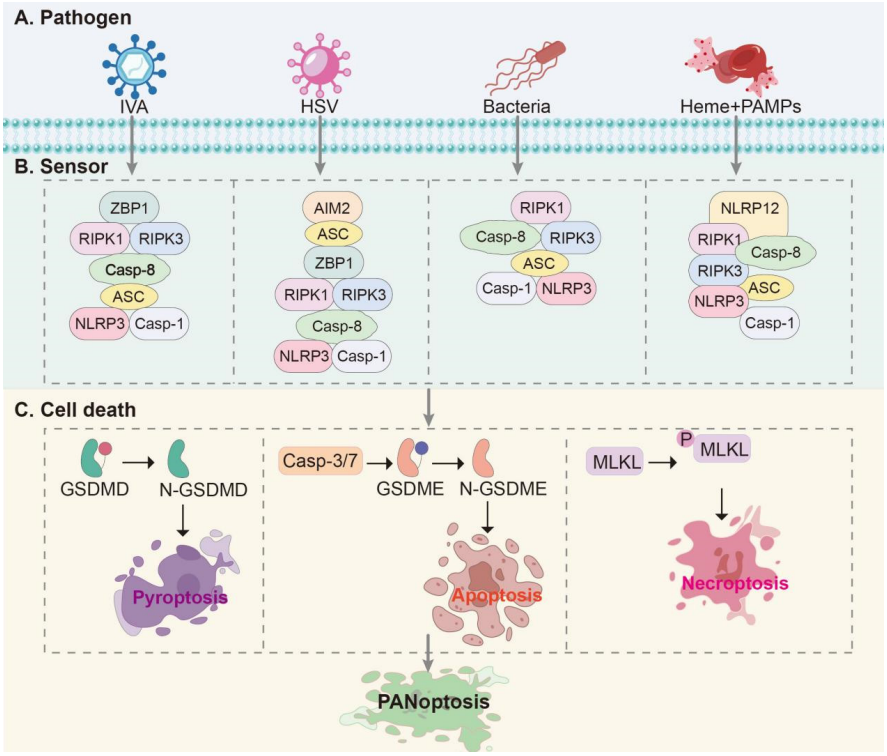

Figure 4. Pathogen-specific activation of integrated cell death pathways via distinct sensor molecules. Schematic model illustrating how diverse pathogens engage specific sensor proteins to trigger an integrated cell death response. (A) Pathogens. Various pathogenic stimuli, including IVA, HSV, bacteria, and heme together with PAMPs, can initiate the signaling cascade. (B) Sensors. Each pathogen or stressor is detected by specific intracellular or extracellular sensor molecules, such as ZBP1 for IAV, AIM2 for viral/bacterial DNA, and RIPK1 for inflammatory signaling. These sensors act as the core molecular platform for signal integration. (C) Cell Death Execution. Activation of the sensor complexes leads to the recruitment and activation of key effector molecules, culminating in the induction of pyroptosis (executed by cleaved GSDMD and its N-terminal fragment, N-GSDMD), apoptosis (mediated by activated Casp-3/7), and/or necroptosis (executed by p-MLKL). This model demonstrates the concept of PANoptosis, where a single sensor complex can coordinately regulate multiple cell death modalities to mount a robust host defense. IVA, Influenza A virus; HSV, Herpes Simplex virus; PAMPs, pathogen-associated molecular patterns; ZBP1, Z-DNA-binding protein 1; AIM2, absent in melanoma 2; RIPK1, receptor-interacting protein kinase 1; RIPK3, receptor-interacting protein kinase 3; NLRP12, NLR family pyrin domain containing 12; NLRP3, NLR family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; Casp-8, caspase-8; Casp-1, caspase-1; MLKL, mixed lineage kinase domain-like pseudokinase; Casp-3/7, caspase-3/7; GSDMD, gasdermin D; N-GSDMD, N-terminal fragment of gasdermin D; GSDME, gasdermin E; N-GSDME, N-terminal fragment of gasdermin E; p-MLKL, phosphorylated mixed lineage kinase domain-like pseudokinase.

programmed cell death pathway that integrates the features of apoptosis, pyroptosis, and necroptosis. The activation of PANoptosis is typically mediated by the PANoptosome complex, which contains various proteins capable of responding to pathogen or damage-associated signals [162]. While pathogens are being cleared, PANoptosis also releases a large number of inflammatory mediators, thereby playing a role in the pathophysiological processes of various diseases, such as infection, autoimmune diseases, and cancer.

The initiation of NETosis is usually triggered by PAMPs or DAMPs, which bind to receptors on the surface of neutrophils, activating intracellular signaling pathways [160]. Subsequently, ROS are produced in large quantities. The production of ROS is a critical step in the process of NETosis. ROS promote chromatin decondensation and the rupture of the cell membrane by oxidizing cellular components [163]. PAD4 mediates histone citrullination, leading to chromatin decondensation and creating conditions for the formation of NETs [164]. Ultimately, the neutrophil cell membrane ruptures, releasing NETs containing DNA, histones, and granular proteins. The DNA and granular proteins in NETs possess antimicrobial activity, directly killing pathogens [165]. Therefore, the primary function of NETs is to capture and kill pathogens such as bacteria and fungi, thereby limiting the spread of infection. However, NETs can interact with monocytes/macrophages, stimulating them to release inflammatory factors, such as IL-1β and TNF-α [166]. Furthermore, NETs can activate the complement system, further amplifying the inflammatory response [167]. Moreover, proteases in NETs (such as neutrophil elastase) can directly destroy tissue structures. Excessive NETosis can lead to the deposition of NETs in tissues, causing tissue damage [168]. This is also why NETosis is considered a culprit in various inflammatory diseases. The role of NETosis in autoimmune diseases will be elaborated in detail later in this text.

PANoptosis can be triggered by various signals, including PAMPs, DAMPs, and cytokines. These signals are recognized by cells through different PRRs, initiating downstream signaling pathways. Upon signal activation, PANoptosome complexes form within cells [169]. Different PANoptosome complexes contain different sensors and adaptor proteins, such as ZBP1, AIM2, and RIPK1 [21]. Upon PANoptosome activation, the execution mechanisms of apoptosis, pyroptosis, and necroptosis are simultaneously initiated. This includes caspase activation, GSDMD-mediated cell membrane perforation, and MLKL-mediated cell membrane disruption [170]. All processes are shown in **Figure 4**. PANoptosis can regulate inflammatory responses through multiple pathways. On the one hand, PANoptosis can induce the death of infected cells, thereby clearing pathogens and limiting infection spread.

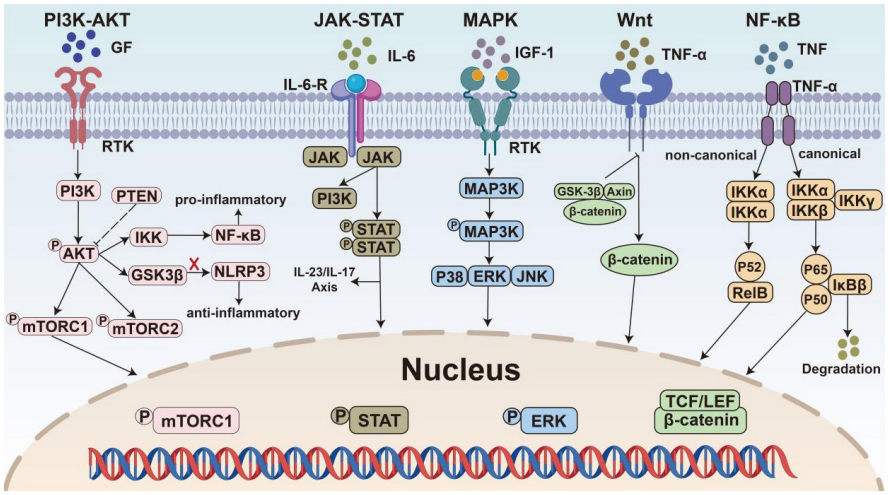

Figure 5. An integrated network of core signaling pathways governing inflammation and cell fate. Schematic model depicting the interplay between five pivotal signal transduction pathways: PI3K-AKT, JAK-STAT, MAPK, Wnt, and NF-κB. The diagram is spatially organized with the plasma membrane (top) and nucleus (bottom) to illustrate the signal flow from extracellular ligand-receptor binding to nuclear gene regulation. Key ligands, including GFs, cytokines (e.g., IL-6, TNF-α), and others, bind to their respective receptors (e.g., RTKs, IL-6 receptor), initiating intracellular cascades. The model highlights critical pathway components, their activation (e.g., phosphorylation of AKT, STAT, ERK, IκB), and nuclear translocation of transcription factors (e.g., NF-κB, STAT, β-catenin). Importantly, it emphasizes extensive cross-talk between pathways, such as the regulatory node of GSK3β, the IL-23/IL-17 axis, and feedback mechanisms (e.g., PTEN inhibition of PI3K). This integrated view provides a framework for understanding how cells coordinate diverse signals to regulate survival, proliferation, inflammatory responses, and gene expression programs. PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; JAK, Janus kinase; STAT, signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; Wnt, Wingless/Integrated; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; GF, growth factor; IL-6, interleukin-6; IGF-1, insulin-like growth factor 1; TNF-α, tumor necrosis factor-alpha; TNF, tumor necrosis factor; IL-6-R, interleukin-6 receptor; RTK, receptor tyrosine kinase; PTEN, phosphatase and tensin homolog; PI3K, phosphoinositide 3-kinase; MAP3K, mitogen-activated protein kinase kinase kinase; GSK-3β, glycogen synthase kinase-3β; IKK, inhibitor of nuclear factor kappa-B kinase; IKKα, inhibitor of nuclear factor kappa-B kinase subunit alpha; IKKβ, inhibitor of nuclear factor kappa-B kinase subunit beta; IKKγ, inhibitor of nuclear factor kappa-B kinase subunit gamma; mTORC1, mechanistic target of rapamycin complex 1; mTORC2, mechanistic target of rapamycin complex 2; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; P38, p38 mitogen-activated protein kinase; RelB, v-rel reticuloendotheliosis viral oncogene homolog B; P50, NF-κB p50 subunit; P52, NF-κB p52 subunit; P65, NF-κB p65 subunit; IκB, inhibitor of NF-κB; NLRP3, NLR family pyrin domain containing 3; IL-23, interleukin-23; IL-17, interleukin-17; TCF, T-cell factor; LEF, lymphoid enhancer-binding factor.

On the other hand, PANoptosis also releases a large number of inflammatory mediators, exacerbating the inflammatory response [171]. In pulmonary arterial hypertension, pulmonary vascular remodeling is the main pathological change, and PANoptosis is closely related to the abnormal death of pulmonary vascular cells and perivascular inflammation [172]. Activation of PANoptosis leads to immune cell adhesion and inflammatory mediator release, further exacerbating vascular remodeling.

3 REGULATORY NETWORK OF INFLAMMARY RESPONSE

Inflammation is a complex biological response made by the body to injury or infection, aimed at eliminating harmful stimuli and initiating tissue repair processes. This process involves various cell types, molecules, and signaling pathways, requiring precise regulation to prevent excessive inflammatory responses, which can lead to further tissue damage and chronic diseases [173]. The triggering of inflammation relies on the molecular recognition of danger signals and the complex mechanisms of action of inflammatory mediators. The body recognizes PAMPs and DAMPs through PRRs. PAMPs are conserved structures shared by microorganisms, such as LPS, peptidoglycan, and flagellin, indicating the presence of infection [174]. DAMPs are endogenous molecules released when cells are damaged or die, including HMGB1, heat shock proteins, and ATP, suggesting tissue damage or cellular stress [175, 176]. PRRs include TLRs, NOD-like receptors (NLRs), C-type lectin receptors (CLRs), and RIG-I-like receptors (RLRs) [177-179]. For example, TLR4 recognizes LPS, activating MyD88-dependent and -independent signaling pathways, leading to the activation of NF-κB and IRF3, ultimately promoting the production of pro-inflammatory cytokines and type I interferons. NLRs are intracellular receptors, recognizing PAMPs and DAMPs within the cytoplasm. The NLRP3 inflammasome is the most extensively studied NLR, which can be activated by various stimuli, including ATP, urate crystals, and amyloid-beta, leading to the activation of caspase-1 and the release of IL-1β and IL-18. CLRs primarily recognize carbohydrate structures on the surface of pathogens and are involved in antifungal immunity. RLRs recognize viral RNA, activate MAVS-mediated signaling pathways, and induce the production of type I interferons, thereby resisting viral infection.

After PRR activation, downstream signaling pathways are activated, leading to the production and release of inflammatory mediators. Inflammatory signaling pathways can be divided into classical and non-classical pathways, which interact with each other to jointly regulate various aspects of the inflammatory response, as shown in **Figure 5**. Classical inflammatory

signaling pathways play a central role in regulating inflammatory responses, mainly including the NF-κB pathway, JAK-STAT pathway, and MAPK pathway. The NF-κB pathway is a key regulatory factor in inflammatory responses [180]. Various stimuli, such as pathogens, pro-inflammatory cytokines (e.g., TNF-α, IL-1β), and oxidative stress, can activate the NF-κB pathway. After ligands bind to TLR receptors on the cell surface, intracellular signal transduction is activated, leading to the activation of the IκB kinase complex. The activated IκB kinase complex phosphorylates IκB proteins, leading to IκB protein degradation and the release of NF-κB dimers (typically p65/p50). The released NF-κB dimers then translocate into the cell nucleus and bind to the promoter regions of target genes. This binding regulates the transcription of downstream genes, including pro-inflammatory cytokines (such as TNF-α, IL-1β, IL-6), chemokines, and adhesion molecules. Activation of the NF-κB pathway plays a crucial role in the initiation and amplification of inflammatory responses. Recent studies have shown that overactivation of the NF-κB pathway is closely associated with the development and progression of various diseases, including atherosclerosis, IBD, and cancer [181, 182]. Negative regulation of NLRs can alleviate inflammation through the NF-κB signaling pathway in IBD. Therefore, the NF-κB pathway is an important target for treating inflammation-related diseases. The JAK-STAT pathway is the main route for cytokine signaling. After cytokines (e.g., interferons, interleukins) bind to cell surface receptors, receptor-associated JAK kinases are activated [183]. Activated JAK kinases phosphorylate STAT proteins, leading to STAT protein dimerization and translocation into the nucleus. In the nucleus, STAT dimers bind to target gene promoters, regulating gene transcription. The JAK-STAT pathway is involved in regulating various immune and inflammatory responses, including cell proliferation, differentiation, and apoptosis. Studies have shown that the JAK-STAT pathway plays an important role in the pathogenesis of chronic inflammatory diseases (such as RA and IBD) [184, 185]. Therefore, inhibiting the JAK-STAT pathway is one of the effective strategies for treating these diseases. The MAPK pathway is a conserved signal transduction pathway involved in regulating various cellular physiological processes, including cell growth, differentiation, stress response, and inflammation [112]. The MAPK pathway includes three major sub-pathways: ERK, JNK, and p38 MAPK. These sub-pathways are activated by various intracellular and extracellular stimuli, such as growth factors, cytokines, oxidative stress, and ultraviolet radiation. The activated MAPK pathway regulates gene transcription and protein synthesis by phosphorylating downstream target proteins, thereby affecting inflammatory responses.

In addition to classical pathways, non-classical inflammatory signaling pathways play important roles in inflammation regulation, primarily including the NLRP3 inflammasome pathway and the Wnt/β-catenin pathway. The NLRP3 inflammasome is an intracellular multiprotein complex that plays a crucial role in innate immune responses [186]. It is composed of NLRP3 protein, adaptor protein ASC, and effector molecule caspase-1 [187]. The activated NLRP3 inflammasome recruits ASC protein and pro-caspase-1 to form a complex, activating caspase-1. Activated caspase-1 cleaves pro-IL-1β and pro-IL-18, generating mature IL-1β and IL-18, which are then released into the extracellular space. IL-1β and IL-18 are potent pro-inflammatory cytokines that can further activate immune cells and promote inflammatory responses. Overactivation of the NLRP3 inflammasome is associated with various inflammatory diseases, including autoimmune diseases and metabolic diseases, which will be discussed in detail in Section 5 [188]. The Wnt/β-catenin pathway was initially thought to play a role in embryonic development and cell differentiation, but recent studies have found that it also plays an important role in inflammatory responses [189]. In the absence of Wnt ligands, β-catenin protein in the cytoplasm is phosphorylated by a complex consisting of antigen-presenting cell (APC), Axin, and GSK-3β, and subsequently ubiquitinated for degradation. When Wnt ligands bind to Frizzled receptors on the cell surface, this binding activates Dishevelled protein, inhibiting the activity of the β-catenin degradation complex, leading to the accumulation of β-catenin in the cytoplasm. The accumulated β-catenin enters the cell nucleus, binds to transcription factors T-cell factor/lymphoid enhancer-binding factor, activating the transcription of downstream target genes, including genes involved in cell proliferation, differentiation, and inflammation. The Wnt/β-catenin pathway is involved in regulating cytokine production, inflammatory cell infiltration, and tissue remodeling, among other processes. Similar to other inflammatory signaling pathways, the Wnt/β-catenin pathway has been increasingly recognized by researchers for its role in the pathogenesis of chronic inflammatory diseases such as osteoarthritis [190]. Drug development targeting these signaling pathways provides new strategies for treating various inflammation-related diseases.

Inflammatory mediators are key molecules in inflammatory responses, including cytokines, chemokines, lipid mediators, and ROS. They participate in the initiation, amplification, and resolution of inflammatory responses through different mechanisms. Cytokines are small protein molecules produced by immune and non-immune cells, playing various roles in inflammatory responses [191]. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 can activate endothelial cells, promote leukocyte recruitment, enhance vascular permeability, and induce the production of other inflammatory mediators. Anti-inflammatory cytokines such as IL-10 and TGF-β inhibit inflammatory responses through mechanisms such as inhibiting the production of pro-inflammatory cytokines and promoting the differentiation of regulatory T cells (Treg), thereby helping inflammation subside and promoting tissue repair [192]. Chemokines are a class of small molecule cytokines whose main function is to guide immune cells to migrate to inflammatory sites. Chemokines, by binding to G protein-coupled receptors on the cell surface, activate intracellular signaling pathways, regulating cell migration, adhesion, and activation [179].

For example, MCP-1/CCL2 can recruit monocytes and macrophages to inflammatory sites, participating in the clearance and repair of inflammatory responses. Lipid mediators are a class of inflammatory mediators derived from the metabolism of unsaturated fatty acids such as AA. AA is produced when phospholipase A2 acts on cell membrane phospholipids. These mediators include prostaglandins, leukotrienes, and lipoxins [193]. Prostaglandins, by activating different prostaglandin receptor subtypes, are involved in regulating inflammatory responses such as vasodilation, vascular permeability, pain, and fever. Leukotrienes are mainly produced by leukocytes and can promote increased vascular permeability, bronchoconstriction, and leukocyte recruitment. Lipoxins, on the other hand, are a class of lipid mediators with anti-inflammatory and pro-resolving effects, capable of inhibiting neutrophil recruitment, promoting macrophage phagocytosis, and accelerating the resolution of inflammation. ROS are a class of oxidatively active molecules produced during inflammatory responses, including superoxide anion, hydrogen peroxide, and hydroxyl radicals, among others [194]. At low concentrations, ROS can act as signaling molecules, participating in the regulation of cell proliferation, differentiation, and apoptosis. However, at high concentrations, ROS can damage intracellular DNA, proteins, and lipids, leading to cell death and tissue damage, and exacerbating inflammatory responses.

The interactions among inflammatory mediators are highly complex, forming an intricate regulatory network. The balance between pro-inflammatory mediators and anti-inflammatory mediators determines the intensity and duration of the inflammatory response. At various stages of the inflammatory response, different types of inflammatory mediators play distinct roles. The initiation and amplification phases of the inflammatory response are primarily dominated by pro-inflammatory mediators, such as TNF-α, IL-1β, and IL-6 [195]. In contrast, inflammation resolution is an active, highly regulated process aimed at eliminating the inflammatory response and restoring tissue homeostasis [196]. As inflammation progresses, pro-inflammatory signaling pathways are gradually suppressed. The activity of the NF-κB pathway is subject to negative feedback regulation, and the production of pro-inflammatory cytokines decreases. The production of anti-inflammatory mediators such as IL-10 and TGF-β increases, further suppressing the pro-inflammatory response. Among these, the production of specialized pro-resolving mediators (SPMs) plays an important role. SPMs are a class of lipid mediators derived from omega-3 fatty acids, including lipoxins, resolvins, protectins, and maresins [197]. SPMs promote neutrophil apoptosis and macrophage phagocytosis, reduce neutrophil recruitment, and inhibit the production of pro-inflammatory cytokines. During inflammation resolution, macrophages polarize from M1 to M2 [198]. M2 macrophages produce anti-inflammatory cytokines such as IL-10 and TGF-β, promoting tissue repair and angiogenesis. Impaired inflammation resolution is closely related to the pathogenesis and progression of various diseases. In atherosclerosis, failed inflammation resolution leads to chronic vascular inflammation, promoting plaque formation and progression [199]. In obesity, persistent adipose tissue inflammation leads to insulin resistance and type 2 diabetes [47]. In summary, the regulatory network of the inflammatory response is a complex and highly coordinated system, involving the synergistic action of multiple signaling pathways and cell types, aiming to achieve effective defense against injury and infection while preventing damage to the body from excessive inflammation.

4 RECIPROCAL REGULATION OF CELL DEATH AND INFLAMMATION

The molecular decoding of cell death-driven inflammatory responses reveals that various cell death modalities release DAMPs. These DAMPs initiate inflammatory responses by binding to PRRs in a mechanism as precise as a "key-lock" match, as shown in **Table 2**. Necroinflammation is the process by which cell death, under physiological or pathological conditions, releases highly immunogenic intracellular molecules and organelles into the interstitial space, thereby triggering a strong immune response [211]. After cell death, the DAMPs released due to the disruption of cell membrane integrity are diverse, including HMGB1, ATP, uric acid, IL-1α, S100 proteins, and mitochondria-derived DAMPs (e.g., mitochondrial DNA, N-formyl peptides) [212]. These molecules have specific physiological functions intracellularly, but upon release to the extracellular space, they act as "danger signals" activating the immune system. Notably, different cell death modalities (e.g., apoptosis, necrosis, pyroptosis, necroptosis) release varying types and quantities of DAMPs, which directly affects the intensity of the inflammatory response. For example, apoptosis typically releases fewer DAMPs, resulting in weak inflammation; whereas necrosis and pyroptosis release large amounts of DAMPs, triggering strong inflammation [17]. Immune cells sense these DAMPs via PRRs. The PRR family includes TLRs, NLRs, RLRs, and CLRs, among others. The binding of DAMPs to specific PRRs is highly selective, similar to a "key-lock" mechanism. For example, HMGB1 and S100 proteins can bind to TLR4, and the HMGB1-TLR4 interaction activates the NF-κB pathway [213]. ATP and uric acid mainly activate the intracellular receptor NLRP3, which in turn triggers inflammasome assembly, caspase-1 activation, and the maturation and release of IL-1β/IL-18 [214]. Mitochondrial DNA, on the other hand, can be recognized by TLR9. This specific recognition ensures the initiation of corresponding immune responses against different damage signals, thereby activating signaling pathways such as NF-κB, MAPK, and IRF, ultimately leading to the production of inflammatory mediators like cytokines and chemokines [215]. This inflammatory microenvironment initiated by the DAMPs-PRRs axis lays the foundation for the subsequent regulation of cell death patterns.

Building upon the aforementioned inflammation initiation mechanisms, key cytokines such as TNF-α and IFN-γ form a

Table 2. Precision recognition of host-derived DAMPs by PRRs and disease cascades

Released DAMPs	Recognition receptor (s)	Downstream pathway	Activated inflammatory mediators	Cell death feedback mechanism	Disease dysregulation	References
HMGB1	TLR4, RAGE	MyD88/ TRIF→NF-κB	TNF-α, IL-6	Necroptosis (RIPK3 activation)	Spinal cord injury	[200]
Mitochondrial DNA (mtDNA)	TLR9, cGAS	STING→IRF3/ NF-κB	IFN-α/β, CXCL10	Mitochondrial apoptosis (BAX/BAK activation)	Lupus nephritis (SLE)	[201]
ATP	P2X7R	NLRP3 inflammasome activation	IL-1β, IL-18	Triggers pyroptosis (GSDMD pore formation)	Gout	[69]
Monosodium urate crystals	NLRP3 (Direct activator)	NLRP3 inflammasome activation	IL-1β, Neutrophil infiltration	Crystal phagocytosis→Lysosomal rupture→Necrosis	Gouty joint erosion	[202]
S100A8/A9	TLR4, RAGE	NF-κB/p38 MAPK	CXCL1, GSDMD pore formation	GSDMD pore formation	RA bone destruction	[203]
Oxidized phospholipids	CD36/TLR4	NLRP3 activation	TNF-α, IL-6	Lipid peroxidation, Ferroptosis	NASH liver fibrosis	[204]
Heat shock protein 70 (HSP70)	TLR2/4, LOX-1	MyD88→NF-κB	CD80/86	Inhibits apoptosis (HSP70-Bax binding)	Tumor immune evasion	[205]
Heparan sulfate fragments	TLR4, CXCR3	TRIF→IRF3	NETs formation→TLR9-IFN-I loop activation	NETs formation	Sepsis microthrombi	[206]
Citrullinated histones	TLR2/4, FcγR	FcγR→Complement activation	Anti-dsDNA	Induces NETosis	Lupus nephritis (SLE)	[207]
Fibronectin fragments	α5β1 integrin	FAK-Src→NF-κB	α-SMA, TGF-β→Induces EMT	Induces EMT	Liver fibrosis	[208]
Mitochondrial cardiolipin	NLRP3	NLRP3 inflammasome activation	IL-1β	Promotes mPTP opening→Initiates apoptosis	Sepsis ARDS	[209]
Endogenous retroviral elements	TLR7, MDA5	MAVS→IRF7	IFN-α	Activates ZBP1-PANoptosis	SLE	[210]

Note: DAMPs, damage-associated molecular patterns; PRRs, pattern recognition receptors; HMGB1, high mobility group box 1; TLR4, Toll-like receptor 4; RAGE, receptor for advanced glycation end products; MyD88, myeloid differentiation primary response 88; TRIF, TIR-domain-containing adapter-inducing interferon-β; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; RIPK3, receptor-interacting protein kinase 3; mtDNA, mitochondrial DNA; TLR9, Toll-like receptor 9; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; IRF3, interferon regulatory factor 3; IFN-α/β, interferon-alpha/beta; CXCL10, C-X-C motif chemokine ligand 10; BAX, BCL2-associated X protein; BAK, BCL2-antagonist/killer 1; SLE, systemic lupus erythematosus; ATP, adenosine triphosphate; P2X7R, P2X purinoceptor 7; NLRP3, NLR family pyrin domain containing 3; IL-1β, interleukin-1β; IL-18, interleukin-18; GSDMD, gasdermin D; S100A8/A9, S100 calcium-binding protein A8/A9; p38 MAPK, p38 mitogen-activated protein kinase; CXCL1, C-X-C motif chemokine ligand 1; RA, rheumatoid arthritis; CD36, cluster of differentiation 36; NASH, non-alcoholic steatohepatitis; HSP70, heat shock protein 70; TLR2, Toll-like receptor 2; LOX-1, lectin-type oxidized LDL receptor 1; CD80/86, cluster of differentiation 80/86; CXCR3, C-X-C chemokine receptor type 3; NETs, neutrophil extracellular traps; IFN-I, type I interferon; FcγR, Fc gamma receptor; anti-dsDNA, anti-double-stranded DNA antibody; α5β1 Integrin, alpha5 beta1 integrin; FAK, focal adhesion kinase; Src, proto-oncogene tyrosine-protein kinase Src; α-SMA, alpha-smooth muscle actin; TGF-β, transforming growth factor-beta; EMT, epithelial-mesenchymal transition; mPTP, mitochondrial permeability transition pore; ARDS, acute respiratory distress syndrome; TLR7, Toll-like receptor 7; MDA5, melanoma differentiation-associated protein 5; MAVS, mitochondrial antiviral signaling protein; IRF7, interferon regulatory factor 7; ZBP1, Z-DNA-binding protein 1.

precise regulatory network in inflammatory responses. Through their concentration gradients, tissue-specific distribution, and synergistic effects with other factors, this network profoundly influences the decision-making logic of cell death patterns (e.g., apoptosis, necroptosis, pyroptosis), thereby shaping the progression and outcome of inflammation. Concentration-dependent regulation is a core feature of this network. Taking TNF-α as an example, its signal output exhibits significant concentration dependence. Under low concentration conditions, TNF-α primarily activates the NF-κB pathway to promote cell survival and inflammatory gene expression [216]. However, when concentrations increase or when specific signal interference is present, such as when caspase-8 activity is inhibited, TNF-α can effectively induce caspase-8-dependent apoptosis or RIPK1/RIPK3/MLKL-mediated necroptosis [217]. Among these, the phosphorylation status of RIPK1 is a critical molecular switch for sensing signal intensity and determining cell fate towards survival, apoptosis, or necroptosis

[91]. Synergism is another important mechanism. IFN-γ itself can regulate immune cell function through the JAK-STAT pathway, such as the enhancement of macrophage bactericidal activity, dendritic cell (DC) antigen presentation, and $CD8^+$ T cell cytotoxicity [218]. However, its core function lies in significantly "sensitizing" cells to other death signals. IFN-γ can greatly enhance cellular sensitivity to factors like TNF-α, collectively promoting the occurrence of apoptosis or necroptosis. This synergistic effect is particularly prominent under pathological conditions; in the cytokine storm induced by SARS-CoV-2 infection, the synergy of TNF-α and IFN-γ can induce PANoptosis, leading to severe tissue damage [219]. The tissue microenvironment, in turn, provides a third dimension of regulation. The ultimate cellular response to TNF-α and IFN-γ signals is not isolated but profoundly depends on the surrounding tissue environment. The influence of the tissue microenvironment on cell death patterns has its molecular basis deeply rooted in the response of subcellular structures. Mitochondria, as primary sensors of microenvironmental stress (e.g., hypoxia, nutrient deprivation), have their functional status (energy production, ROS levels, membrane integrity) directly determining whether cells undergo apoptosis or trigger a strong inflammatory response [220]. The endoplasmic reticulum, in turn, senses protein synthesis burden and folding stress in the microenvironment, and the intensity and duration of its stress response regulate the cell death threshold and inflammatory cytokine secretion [221]. The nucleus integrates signals from the microenvironment (e.g., genotoxic stress), influencing the local inflammatory environment by activating p53-mediated apoptosis or regulating inflammation-related gene networks [222]. More importantly, the ubiquitination modification system, as a highly plastic regulatory layer, can dynamically modify key proteins (e.g., RIPK1, NF-κB pathway components) based on microenvironmental cues, finely tuning cellular sensitivity to death signals and the intensity and nature of the inflammatory response [223]. Therefore, understanding the functional changes in mitochondria, endoplasmic reticulum, and nucleus, as well as the dynamic regulation of the ubiquitination network, is key to elucidating how the tissue microenvironment shapes cell death patterns and their accompanying inflammatory responses. Therefore, understanding how inflammatory signals, particularly TNF-α and IFN-γ, precisely regulate cell death patterns through concentration gradients, synergistic effects, and integration with the tissue microenvironment, is crucial for uncovering the pathogenesis of inflammation-related diseases and developing targeted intervention strategies. This multilevel regulatory network enables a tight coupling between cell death and inflammation. It is precisely this bidirectional interaction mechanism that provides the molecular basis for the formation of the death-inflammation feedback loop.

In the pathological processes of various diseases, the death-inflammation feedback loop plays a core driving role, characterized by a self-amplifying cycle formed between cell death events and inflammatory responses. Among these, the pyroptosis-NLRP3 cascade amplification loop, the NETosis-IFN-α reciprocal promotion loop, and the PANoptosis integrated cell death pathway are key components of this circuit and also potential therapeutic targets. The pyroptosis-NLRP3 positive feedback loop begins with NLRP3 inflammasome-mediated caspase-1 activation, which cleaves GSDMD protein to form plasma membrane pores, executing the pyroptosis process and releasing pro-inflammatory factors such as IL-1β and IL-18 [224]. A critical turning point is that the released DAMPs can trans-activate NLRP3 inflammasomes in adjacent cells, thereby forming a "pyroptosis-DAMPs release-NLRP3 re-activation" cyclic amplification pathway. This loop is particularly prominent in acute inflammatory conditions such as sepsis and gout. Targeted intervention strategies, such as the NLRP3 inhibitor MCC950 or the caspase-1 inhibitor VX-765, can inhibit the cascade reaction by blocking the initial steps of the loop [225]. The NETosis-IFN-α reciprocal loop demonstrates an intercellular synergistic effect. Neutrophils release NETs via NETosis, thereby activating plasmacytoid DCs through PRRs such as TLR9 and inducing abundant production of IFN-α. Notably, IFN-α upregulates the expression of PAD4 via the JAK-STAT signaling pathway, promoting histone citrullination and chromatin decondensation, thereby enhancing the propensity for neutrophil NETosis and forming an intercellular signaling closed loop [226]. This loop plays a central role in autoimmune diseases such as SLE, and DNase I degradation of NETs or JAK inhibitors blocking IFN signaling can effectively break the cycle [227]. The PANoptosis integrative death pathway represents a higher-level regulatory mode. Mediated by sensor proteins such as ZBP1 and AIM2, the assembly of adaptor molecules such as RIPK1 forms the PANoptosome multiprotein complex platform, which is unique in its ability to simultaneously activate caspase-1, caspase-8, and RIPK3 pathways [228]. This synergistic effect leads to a mixed death phenotype and the release of a large amount of DAMPs, inducing a systemic inflammatory storm. In severe COVID-19 infection and hemophagocytic syndrome, targeting key nodes such as ZBP1 can disrupt complex assembly, providing new insights for curbing lethal inflammation [229].

5 DYSREGULATED INTERACTION BETWEEN CELL DEATH AND INFLAMMATION IN DISEASE CONTEXTS

Under physiological conditions, the interaction between cell death and inflammation constitutes a delicate balance: apoptotic cells are promptly cleared and release anti-inflammatory factors to promote tissue repair, whereas controlled pro-inflammatory cell death, such as pyroptosis, assists in pathogen clearance. However, when genetic susceptibility, pathogen invasion, or metabolic disorders disrupt this balance, characteristic dysregulation of this interaction is triggered. In autoimmune diseases, defective clearance of dead cells leads to persistent exposure of nuclear antigens, such as citrullinated histones. This exposure, via cGAS-STING or TLR9 pathways, induces a type

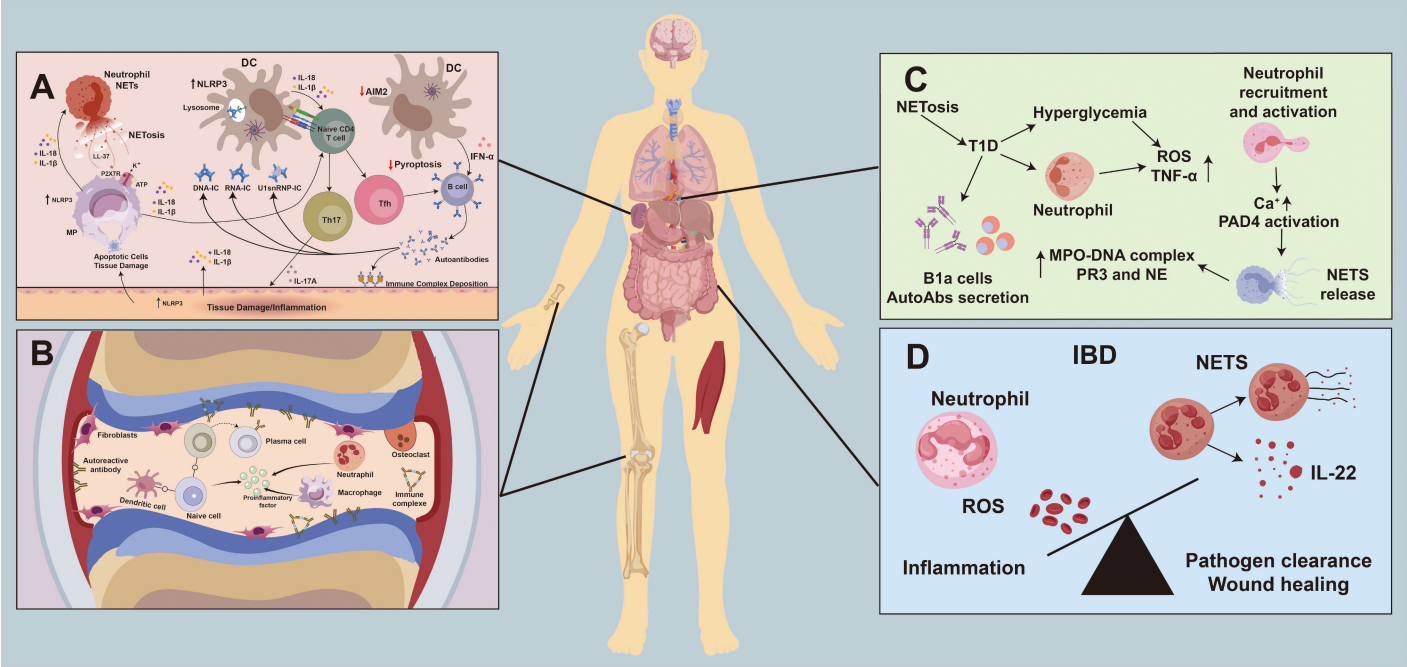

Figure 6. The multifaceted roles of neutrophils in tissue homeostasis and disease pathogenesis. Schematic summary of neutrophil functions across distinct physiological and pathological contexts. (A) Neutrophil interaction with adaptive immunity in tissue damage. Neutrophils engage in bidirectional crosstalk with DCs and Th cells, undergoing NETosis and releasing cytokines (e.g., IL-1β, IL-18 via pyroptosis), which can amplify inflammatory responses and influence T cell polarization. (B) Neutrophil involvement in the arthritic joint microenvironment. Neutrophils are present alongside plasma cells, fibroblasts, and immune complexes, contributing to chronic inflammation and tissue destruction through the release of proteases and ROS. (C) Mechanism of NETosis in T1D. In a hyperglycemic milieu, neutrophils are activated by ROS and TNF-α, leading to the release of NETs containing MPO-DNA complexes. This process is implicated in β-cell damage and the propagation of autoimmunity. (D) Dual role of neutrophils in IBD. Neutrophils exhibit a Janus-faced function: they drive tissue damage through robust ROS production but also contribute to mucosal healing and host defense via the secretion of IL-22, highlighting their context-dependent role in resolving inflammation. NET, neutrophil extracellular trap; IL-1β, interleukin-1β; IL-37, interleukin-37; P2X7R, P2X purinoceptor 7/P2X7 receptor; ATP, adenosine triphosphate; NLRP3, NLR family pyrin domain containing 3; MP, macrophage; DC, dendritic cell; DNA-IC, DNA-containing immune complex; RNA-IC, RNA-containing immune complex; U1snRNP-1C, U1 small nuclear ribonucleoprotein-immune complex; IL-17A, interleukin-17A; Th, T helper cell; Th17, T helper 17 cell; AIM2, absent in melanoma 2; IFN-α, interferon-alpha; T1D, type 1 diabetes; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha; B1a cells, B-1a lymphocytes; autoAbs secretion, autoantibodies secretion; MPO-DNA, myeloperoxidase-DNA complex; PR3, proteinase 3; NE, neutrophil elastase; PAD4, peptidylarginine deiminase 4; IBD, inflammatory bowel disease; IL-22, interleukin-22; IL-18, interleukin-18.

I interferon storm, driving autoimmune attacks. In infectious diseases, pathogens directly manipulate cell death programs, inducing necroptosis or PANoptosis cascades, which release excessive DAMPs and ignite systemic inflammatory responses. In metabolic diseases, nutritional stress can shift protective apoptosis towards pro-inflammatory pyroptosis or ferroptosis, forming a vicious cycle of chronic inflammation and metabolic dysfunction. However, the perioperative period—characterized by surgical stress, ischemia-reperfusion injury, and anesthetic exposure—can profoundly disrupt this equilibrium, accelerating or unmasking subclinical pathologies. This article will systematically analyze the unique mechanisms of cell death-inflammation axis dysregulation in these three types of diseases and discuss their specific implications for perioperative risk stratification, organ protection, and the development of targeted intervention strategies tailored to surgical patients.

5.1 Autoimmune diseases

Autoimmune diseases are conditions in which the immune system attacks the body's own tissues, leading to chronic inflammation, tissue damage, and systemic dysfunction. Examples of autoimmune diseases include RA, SLE, type 1 diabetes mellitus (T1DM), and IBD, as shown in **Figure 6**. These diseases affect approximately 10% of the global population, imposing a significant health and economic burden worldwide [230]. The pathogenesis of autoimmune diseases is complex, involving not only genetic susceptibility but also environmental triggers and immune dysregulation. Increasing evidence indicates that dysregulation of the cell death-inflammation axis leads to autoimmune diseases. In SLE, the over-formation of NETs and impaired apoptotic cell clearance lead to the release of autoantigens, activating B cells to produce autoantibodies, which form immune complexes and exacerbate inflammatory

responses [231]. In RA, GSDMD-mediated pyroptosis and the overexpression of IL-1β promote the formation of a synovial inflammatory microenvironment, leading to joint damage [211]. In T1DM, the death of pancreatic beta cells releases autoantigens, activating autoreactive T cells, leading to immune system attack on islet cells [232]. In IBD, ferroptosis of intestinal epithelial cells disrupts the intestinal barrier and exacerbates intestinal inflammatory responses [233]. Patients with autoimmune diseases present unique challenges in the perioperative period, as surgical stress can potentially exacerbate underlying dysregulated immunity and inflammation, increasing the risk of postoperative flares and complications. Therefore, the complex interplay between cell death and inflammation plays a crucial role in the pathogenesis and progression of various autoimmune diseases, and the regulation targeting this axis may offer new strategies not only for the treatment of autoimmune diseases but also for perioperative management to improve surgical outcomes in this vulnerable population.

SLE is a complex autoimmune disease, whose pathological essence lies in a vicious cycle formed between cell death and inflammatory responses [234]. The dysregulation of this complex network begins with abnormal regulation of the apoptotic process. In patients, impaired clearance of apoptotic cells leads to a large accumulation of uncleared cellular debris in tissues. Autoantigens released from these fragments (e.g., DNA, histones) activate the TLR pathway, stimulating plasmacytoid DCs to produce excessive IFN-I, which in turn triggers the differentiation of autoreactive B cells and the production of autoantibodies such as anti-dsDNA antibodies [235, 236]. Notably, this process is intertwined with the abnormal activation of inflammatory cell death pathways. Necroptosis mediates cell membrane rupture via the RIPK3/MLKL pathway, while pyroptosis relies on GSDMD to form plasma membrane pores; both jointly promote the release of pro-inflammatory factors such as IL-1β and IL-18, directly exacerbating tissue inflammation [237]. In the renal tissue of lupus nephritis patients, the abnormally high expression of these inflammatory death markers has been confirmed to be associated with organ damage [238]. Simultaneously, ferroptosis and NETosis play synergistic roles in the immunopathology of SLE [239]. Ferroptosis-driven lipid peroxidation not only directly damages cells but also activates neutrophils and macrophages through its released oxidative stress products, amplifying the inflammatory cascade. Studies have found that inhibiting ferroptosis can alleviate disease progression in SLE mouse models, indicating that ferroptosis plays an important role in the pathogenesis of SLE [238]. Meanwhile, NETs excessively released by neutrophils, as DNA-histone-rich reticular structures, serve both as sources of autoantigens and as participants in immune complex formation. After these complexes deposit in target organs such as the kidneys and skin, they ultimately lead to characteristic lesions like glomerulonephritis and malar rash through complement activation and Fc receptor-mediated inflammatory responses [240]. The latest research further reveals that immunometabolic dysregulation (such as glycolysis/oxidative phosphorylation imbalance) in SLE patients exhibits cross-regulation with cell death pathways [241]. Metabolic disorders can alter immune cell death thresholds, such as by enhancing neutrophil NETosis propensity or reducing macrophage apoptotic clearance capacity, thereby forming a "metabolism-death-inflammation" positive feedback loop. Based on these mechanisms, novel therapeutic strategies focus on multi-target intervention. DNase I degradation of NETs can reduce autoantigen exposure [242]. Ferroptosis inhibitors (such as Liproxstatin-1) can alleviate oxidative stress damage [243]. Small molecule inhibitors targeting RIPK1 or caspase-1 can block inflammatory cell death pathways. These interventions have shown a dual benefit of alleviating renal inflammation and reducing autoantibody levels in preclinical models.

As a chronic inflammatory disease, RA has a pathological process closely related to the complex interplay between cell death and inflammatory responses. Dysregulation of various cell death pathways, including apoptosis, necroptosis, pyroptosis, and ferroptosis, collectively drives characteristic lesions such as synovial inflammation, cartilage destruction, and bone erosion [244]. In the pathogenesis of RA, inhibition of apoptosis in synovial cells leads to abnormal synovial proliferation and persistent inflammation. Necroptosis, on the other hand, releases intracellular contents through cell membrane rupture, amplifying the inflammatory cascade. Notably, IFN-γ can participate in the regulation of inflammatory death by modulating necroptosis [245]. Pyroptosis, as a highly inflammatory form of cell death mediated by caspase-1 activation, promotes the release of pro-inflammatory factors such as IL-1β and IL-18. Among these, macrophage pyroptosis has been confirmed to promote RA progression through mechanisms such as DNA polymerase β deficiency [246]. Ferroptosis is characterized by iron-dependent lipid peroxidation and ROS accumulation, and its association with ROS-dependent apoptosis suggests new pathological dimensions [247]. Dysregulation of these cell death pathways collectively leads to the release of pro-inflammatory mediators, forming a "death-inflammation" vicious cycle. The inflammatory response plays a central role in RA; key pro-inflammatory factors such as TNF-α, IL-1β, and IL-6 directly promote cartilage degradation and bone erosion by activating synovial fibroblasts (FLS) and immune cells [248]. T cells, B cells, macrophages, and FLS constitute a complex immune network. T cells drive pathogenesis via cytokine-dependent and independent mechanisms, while FLS mediate joint destruction by secreting matrix metalloproteinases [249, 250]. Non-coding RNAs (e.g., miR-21) play an important role in inflammation regulation by modulating the Th17/Treg balance and STAT3 signaling pathway [251]. This interplay between cell death and inflammation forms a self-reinforcing axis: dysregulation of death pathways releases pro-inflammatory mediators, and activated immune cells in turn further trigger death programs, ultimately leading to irreversible joint damage.

The core pathological feature of T1DM is the progressive destruction of pancreatic β-cells, a process driven by a vicious cycle between cell death and inflammatory responses [252]. When β-cells die through pathways such as apoptosis, necroptosis, or pyroptosis, the released intracellular antigens act as DAMPs and are recognized by DCs and macrophages, activating the NLRP3 inflammasome pathway and promoting the release of pro-inflammatory factors such as IL-1β and IL-18 [253]. This inflammatory microenvironment not only directly damages β-cell function and inhibits insulin secretion, but also activates autoreactive T and B cells, leading to the production of autoantibodies against β-cell antigens and thus forming a "death-inflammation-autoimmunity" positive feedback loop. Notably, viral infections (e.g., SARS-CoV-2) can exacerbate this process through molecular mimicry mechanisms or direct β-cell damage, while lipid metabolism disorders and miRNA expression dysregulation (e.g., miR-21-mediated gene silencing) participate in disease progression by regulating immune cell function [254, 255]. In the immunopathological network of T1DM, $CD8^+$ T cells directly kill β-cells via the perforin-granzyme pathway, while macrophages amplify the inflammatory cascade by releasing pro-inflammatory mediators and presenting antigens [256]. Autoantibodies produced by B cells not only activate the complement system but also mediate antibody-dependent cell-mediated cytotoxicity, collectively leading to a reduction in β-cell mass [257]. This multicellular collaborative immune attack ultimately triggers metabolic collapse characterized by absolute insulin deficiency.

The pathological essence of IBD lies in the imbalance of intestinal epithelial cell homeostasis, with its core driving factor being a vicious cycle between cell death pathways and inflammatory responses [258]. When programmed cell death pathways such as apoptosis, necroptosis, and pyroptosis are dysregulated, the integrity of the intestinal barrier is compromised. Overactivated necroptosis mediates cell membrane rupture via the RIPK3/MLKL pathway, releasing a large number of pro-inflammatory factors such as IL-1β and TNF-α [259]. Conversely, insufficient apoptotic function leads to the retention of damaged cells, continuously activating innate immune responses. Notably, Gasdermin family protein-mediated pyroptosis is particularly crucial in IBD. The plasma membrane pores formed by caspase cleavage of GSDMD not only promote the maturation and release of IL-1β but also provide an invasion channel for gut microbiota and their metabolites (e.g., short-chain fatty acids), exacerbating mucosal immune dysregulation [260, 261]. This death-inflammation interaction forms a self-reinforcing axis. DAMPs released by cell death activate macrophages and DCs, amplifying inflammatory signals via the NLRP3 inflammasome [262]. In turn, cytokines such as TNF-α and IL-6 induce epithelial cell death via the NF-κB/MAPK pathway. Gut microbiota dysbiosis plays an important role in this process. Overproliferation of Proteobacteria directly damages epithelial tight junctions, while their metabolic products affect the necroptosis threshold by regulating RIPK1 phosphorylation status. Genetic factors (e.g., NOD2 mutations) further promote the accumulation of intracellular PAMPs by weakening autophagic clearance capacity, forming a "microbiota-gene-death" triad that drives an inflammatory storm [263].

Beyond elucidating pathogenesis, understanding these dysregulated pathways informs perioperative risk stratification for patients with autoimmune conditions. For instance, elevated levels of circulating cell-free DNA, potentially originating from NETs, may serve as a biomarker for heightened tissue injury and immune activation, signaling an increased risk for postoperative inflammatory complications. Similarly, specific autoantibodies, such as anti-dsDNA in SLE, not only serve as diagnostic markers but may also correlate with the degree of immune dysregulation and organ vulnerability under surgical stress. This knowledge enables a more nuanced preoperative assessment, moving beyond the disease label to gauge the individual's inflammatory burden and potential for exacerbation. Consequently, perioperative management can be tailored—for example, by considering targeted anti-inflammatory prophylaxis in a patient with high NETosis biomarkers or by adjusting immunosuppressive regimens based on specific cell death pathway activities to mitigate the risk of a postoperative flare.

5.2 Infectious diseases

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection, and its pathogenesis is closely related to the complex relationship between cell death and inflammation. In early sepsis, PAMPs and DAMPs are released, activating PRRs such as TLRs and NLRs. This activation triggers the production of a large number of pro-inflammatory cytokines and chemokines, leading to an excessive inflammatory response [264]. This excessive activation causes widespread tissue damage and vascular leakage [265]. In late sepsis, persistent cell death and chronic inflammation impair immune cell function, leading to immunosuppression. Lymphocyte apoptosis and monocyte exhaustion reduce the body's ability to clear infection, ultimately leading to secondary infections and multiple organ failure [266]. Postoperative sepsis is a major cause of morbidity and mortality, in which the added insults of surgery and anesthesia can amplify these dysregulated pathways. Dysregulation of the cell death-inflammation axis is a key driver of the complex and dynamic immune response in sepsis, as shown in **Figure 7**. Therefore, targeted interventions to restore immune homeostasis are crucial, particularly in the high-stakes perioperative setting.

In the initial phase of sepsis, PAMPs and DAMPs are released from damaged cells, triggering the activation of innate immune cells. Activation of PRRs initiates downstream signaling pathways, leading to the massive production of pro-inflammatory cytokines. These cytokines play a crucial role in the inflammatory response, recruiting immune cells to the site of infection

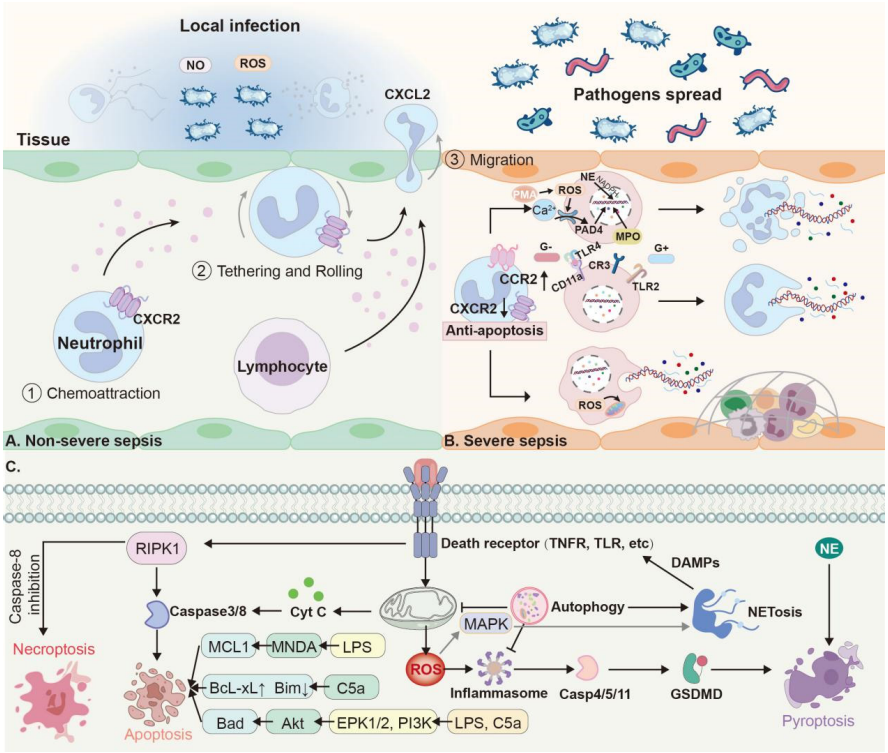

Figure 7. Dysregulated neutrophil responses determine pathological progression from localized infection to severe sepsis. Schematic model contrasting neutrophil dynamics in controlled versus dysregulated immune responses during sepsis. (A) Non-severe sepsis (controlled response). A local infection initiates a coordinated immune response: (1) Chemoattraction: Neutrophils are recruited to the site by chemokines (e.g., CXCL2). (2) Tethering and Rolling: Neutrophils adhere to and roll on the endothelium. (3) Migration: Neutrophils transmigrate into the tissue to clear pathogens, a process potentially aided by lymphocytes. This controlled response prevents systemic pathogen spread. (B) Severe sepsis (dysregulated response). Systemic pathogen dissemination leads to a hyperinflammatory state. Neutrophils exhibit enhanced migration but also exhibit resistance to apoptosis, promoted by survival signals such as increased MCL-1 and Bcl-xL, and activation of pro-survival pathways (e.g., ERK1/2, PI3K/Akt). This prolongs neutrophil lifespan, contributing to collateral tissue damage through excessive release of ROS and proteases like NE. (C) Orchestration of neutrophil cell death pathways. The panel details how specific stimuli (e.g., LPS, C5a, cytokines, DAMPs) and molecular interactions (e.g., caspase-8 inhibition) regulate the balance between distinct neutrophil death modalities, including apoptosis, necroptosis, pyroptosis, and NETosis. This balance critically influences the inflammatory outcome and disease severity. This figure integrates spatial, functional, and molecular perspectives to elucidate how neutrophil fate decisions drive the transition from a protective immune response to a pathological state in sepsis. NO, nitric oxide; ROS, reactive oxygen species; CXCL2, C-X-C motif chemokine ligand 2; CXCR2, C-X-C chemokine receptor type 2; RIPK1, receptor-interacting protein kinase 1; Cyt c, cytochrome c; MCL-1, myeloid cell leukemia 1; MNDA, myeloid cell nuclear differentiation antigen; LPS, lipopolysaccharide; Bad, BCL2-associated agonist of cell death; Akt, protein kinase B; ERK1/2, extracellular signal-regulated kinase 1/2; PI3K, phosphoinositide 3-kinase; C5a, complement component 5a; TNFR, tumor necrosis factor receptor; TLR, Toll-like receptor; DAMPs, damage-associated molecular patterns; MAPK, mitogen-activated protein kinase; Casp4/5/11, caspase-4/5/11; GSDMD, gasdermin D; Bcl-xL, B-cell lymphoma-extra large; NE, neutrophil elastase; NADPH, nicotinamide adenine dinucleotide phosphate; PMA, phorbol 12-myristate 13-acetate; PAD4, peptidylarginine deiminase 4; MPO, myeloperoxidase; CCR2, C-C chemokine receptor type 2; CD11a, cluster of differentiation 11a; TLR4, Toll-like receptor 4; CR3, complement receptor 3; TLR2, Toll-like receptor 2; Bim, BCL-2 interacting mediator of cell death.

and activating other immune cells. However, the excessive release of pro-inflammatory cytokines can lead to SIRS, characterized by fever, tachycardia, tachypnea, and leukocytosis [267]. SIRS may lead to increased vascular permeability, vasodilation, and microthrombus formation, thereby causing tissue hypoxia and organ dysfunction. Pro-inflammatory cytokines can damage endothelial cells, leading to vascular leakage and edema [268]. Endothelial damage also activates the coagulation cascade, leading to thrombus formation in microvessels, further impairing organ perfusion. Furthermore, neutrophils, major innate immune cellS, are massively recruited to the site of infection in early sepsis [269]. Activated neutrophils release proteolytic enzymes and ROS, which further damage tissues. Neutrophils can also undergo NETosis to capture and kill pathogens. However, excessive NETs formation can lead to inflammation and tissue damage.

Although early sepsis is characterized by hyperinflammation, the late stage typically involves an immunosuppressed state. This immunoparalysis renders patients susceptible to secondary infections and persistent organ dysfunction. Sepsis-induced immunosuppression is caused by multiple mechanisms, including immune cell apoptosis, immune cell exhaustion, and the expansion of suppressive immune cells [270]. Apoptosis, or programmed cell death, is an important cause of immune cell depletion in sepsis. T cells, B cells, and DCs undergo apoptosis, reducing the magnitude of the immune response [271]. Pro-inflammatory cytokines, such as TNF-α and IL-1β, and death receptor ligands, such as FasL, are involved in inducing immune cell apoptosis. Immune cell exhaustion also contributes to immunosuppression in sepsis [272]. Prolonged immune activation can lead to immune cell exhaustion, resulting in impaired function and reduced proliferative capacity. Exhausted T cells express inhibitory receptors, such as PD-1, a receptor that suppresses their activity [273]. Tregs and myeloid-derived suppressor cells are suppressive immune cells that inhibit immune responses. In sepsis, Tregs and myeloid-derived suppressor cells expand, further suppressing immune responses and promoting pathogen persistence [274]. Another important aspect of immune cell

dysfunction in sepsis is impaired antigen presentation. APCs, such as DCs and macrophages, play a crucial role in initiating adaptive immune responses [275]. In sepsis, APC function is impaired, leading to reduced antigen presentation and decreased T cell activation. Furthermore, sepsis leads to polarization of cytokine production, characterized by decreased pro-inflammatory cytokines and increased anti-inflammatory cytokines [276]. This cytokine polarization contributes to an immunosuppressive state and impairs the ability to clear infections.

Cell death plays a crucial role in the pathophysiology of sepsis, with several types of cell death involved, including apoptosis, necroptosis, pyroptosis, and autophagy. Apoptosis is a type of programmed cell death, characterized by cell shrinkage, chromatin condensation, and the formation of apoptotic bodies. Apoptosis is generally considered immune silent, as it does not release inflammatory contents [277]. However, in sepsis, excessive apoptosis can lead to immune cell depletion and promote immunosuppression. Necroptosis is mediated by the activation of RIPK1 and RIPK3. In contrast to apoptosis, necroptosis leads to the release of inflammatory mediators, thereby exacerbating the inflammatory response [1]. Pyroptosis is a form of inflammatory cell death, mediated by inflammasome activation and subsequent GSDMD cleavage. Inflammasomes are cytoplasmic multiprotein complexes that activate caspase-1, which cleaves GSDMD, leading to pore formation in the cell membrane and the release of pro-inflammatory cytokines, such as IL-1β and IL-18. Pyroptosis plays a crucial role in the pathophysiology of sepsis, contributing to the inflammatory response and organ dysfunction [278]. Autophagy is a cellular process involving the degradation and recycling of cellular components. Autophagy can play a role in cell survival and cell death, depending on the situation. In sepsis, autophagy has been shown to promote cell survival by clearing damaged organelles and protein aggregates [279]. However, excessive autophagy can lead to autophagic cell death, which is a form of cell death that can aggravate sepsis by disrupting cellular homeostasis and potentially exacerbating the inflammatory response.

Given that the cell death-inflammation axis plays a crucial role in the pathophysiology of sepsis, therapeutic strategies targeting this axis hold promise for improving the prognosis of sepsis patients. These strategies include inhibiting inflammation, modulating cell death pathways, and restoring immune function. Strategies for inhibiting inflammation include the use of anti-inflammatory drugs, such as corticosteroids and TNF-α inhibitors [280]. However, these drugs have limited effectiveness in sepsis and are associated with significant side effects [281]. Strategies to modulate cell death pathways include inhibiting apoptosis, necroptosis, and pyroptosis. Caspase inhibitors can block apoptosis and have been shown to exert protective effects in preclinical studies [282]. RIPK1 inhibitors can block necroptosis and are currently being developed for the treatment of various inflammatory diseases. Strategies to restore immune function include the use of immunostimulants, such as IFN-γ and granulocyte-macrophage colony-stimulating factor [274]. These cytokines can enhance immune cell function and improve pathogen clearance. Additionally, mesenchymal stem cells have been shown to have immunomodulatory effects in sepsis [283]. Mesenchymal stem cells can inhibit the JAK-STAT signaling pathway and regulate Th cells, thereby alleviating the cytokine storm in sepsis.

The principles of risk stratification and targeted intervention are equally critical in the context of perioperative infections and sepsis. The preoperative identification of patients at high risk for infectious complications or sepsis progression can leverage biomarkers of immune status and cellular stress. For example, profiling markers of innate immune activation, such as components of NETs or DAMPs, might identify patients with a subclinical hyperinflammatory state who are primed for an exaggerated response to surgical trauma. Furthermore, the recognition that surgical stress itself can potentiate specific cell death pathways, such as NLRP3 inflammasome-mediated pyroptosis, connects the risk of postoperative sepsis to fundamental mechanisms of tissue damage. In a patient with signs of metabolic stress (e.g., elevated oxidative stress markers), the vulnerability to ferroptosis in critical tissues like the intestinal epithelium or liver could be increased, thereby compromising barrier function and facilitating bacterial translocation. Thus, preoperative optimization might include strategies to bolster cellular resilience, such as antioxidant support in high-risk patients, while postoperative monitoring could focus on biomarkers reflective of specific death pathways (e.g., GSDMD for pyroptosis) to guide timely and mechanism-directed interventions like IL-1 blockade, moving sepsis management towards a more personalized and preemptive model.

5.3 Metabolic diseases

Metabolic diseases, such as non-alcoholic steatohepatitis (NASH) and atherosclerosis, are closely related to the complex relationship between cell death and inflammation. Patients with these conditions are at significantly increased risk for perioperative complications due to their underlying metabolic and inflammatory instability, which can be severely tested by the physiologic stress of surgery. NASH is a chronic liver disease associated with metabolic dysfunction, characterized by hepatic fat accumulation, inflammation, hepatocyte injury, and fibrosis [284]. The pathological core of NASH lies in the "death-inflammation" vicious cycle triggered by lipid metabolism disorder. When lipids excessively accumulate within hepatocytes (hepatic steatosis), toxic lipids such as saturated fatty acids induce endoplasmic reticulum stress and mitochondrial dysfunction, leading to explosive production of ROS [285]. This metabolic stress causes hepatocytes to undergo apoptosis, necroptosis, and GSDMD-mediated pyroptosis, releasing DAMPs such as HMGB1 and ATP. These DAMPs, by activating TLRs on hepatic Kupffer cells and infiltrating macrophages, initiate the NLRP3 inflammasome signaling cascade, driving a

storm of pro-inflammatory factors such as TNF-α and IL-1β [286]. Notably, a chronic inflammatory environment further disrupts metabolic homeostasis. TNF-α exacerbates insulin resistance by inhibiting insulin receptor substrate phosphorylation, while IL-1β directly inhibits fatty acid β-oxidation, forming a positive feedback loop of "lipid accumulation-cell death-inflammation-metabolic dysfunction" [287]. Persistent inflammation activates hepatic stellate cells (HSCs), transforming them into myofibroblasts, which promote the progression of liver fibrosis by secreting ECM components such as type I collagen [288]. In this process, gut microbiota dysbiosis plays a synergistic role. Gut microbiota dysregulation leads to LPS translocation, which, after entering the liver via the portal vein, promotes Kupffer cell activation through TLR4. Meanwhile, reduced short-chain fatty acids weaken the protective function of the intestinal barrier [289].

Atherosclerosis is another chronic inflammatory disease in which lipids accumulate within the arterial walls, leading to plaque formation, which can ultimately result in cardiovascular events [290]. When metabolic diseases such as obesity and diabetes trigger lipid metabolism dysregulation, they can directly induce various forms of cell death, including pyroptosis, apoptosis, and necrosis. These dying cells release a large amount of DAMPs, which, after binding with PRRs, activate downstream inflammatory pathways. Activation of inflammatory responses further exacerbates vascular endothelial damage, increases vascular permeability, and promotes lipid deposition within the arterial wall [291]. Monocytes are recruited to the vascular wall, where they differentiate into macrophages and phagocytose oxidized low-density lipoprotein, forming foam cells [292]. Excessive accumulation of foam cells ultimately leads to cell death, forming a necrotic core. This releases more DAMPs, further exacerbating the inflammatory response and creating a vicious cycle. Furthermore, the inflammatory environment also promotes the proliferation and migration of vascular smooth muscle cells, alters the composition of the ECM, leading to the formation and instability of atherosclerotic plaques [293]. This dysregulation of the axis composed of cell death and inflammation not only directly drives the initiation and progression of atherosclerosis but also causes low-grade inflammation systemically, exacerbating characteristics of metabolic diseases such as insulin resistance. This persistent, low-grade inflammatory activation and plaque instability critically underpin the increased incidence of major adverse cardiovascular events, such as myocardial infarction, in the perioperative period. The physiological stressors of surgery—including catecholamine surges, hemodynamic instability, and a hypercoagulable state—can disrupt vulnerable, inflammation-rich atherosclerotic plaques. This disruption exposes pro-thrombotic material, triggering acute thrombosis and vessel occlusion, especially in plaques where ongoing inflammatory cell death (e.g., macrophage necroptosis) has already weakened the fibrous cap.

Although NASH and atherosclerosis have distinct target organs, they share the core pathological paradigm of "lipid metabolism disorder-triggered cell death-inflammation vicious cycle". At the molecular level, both exhibit saturated fatty acid-induced endoplasmic reticulum stress and mitochondrial dysfunction, events that activate multiple death pathways through ROS burst, thereby releasing DAMPs such as HMGB1/ATP. These danger signals, via the TLR4/NLRP3 axis, amplify the inflammatory cascade, forming a "cell death-inflammation-exacerbation" self-reinforcing loop. Meanwhile, organ-specific effects also shape differences in disease phenotypes. In NASH, HSCs transform into myofibroblasts, driving collagen deposition. In contrast, in atherosclerosis, foam cell necrosis determines plaque stability. This difference stems from microenvironmental specialization. The liver amplifies inflammation via the gut-liver axis (LPS translocation), while the vascular system accelerates endothelial damage through blood flow in conjunction with oxidized low-density lipoprotein deposition. From a systems biology perspective, metabolic diseases are essentially a multi-organ dialogue triggered by the dysregulation of the "death-inflammation axis". Adipose tissue inflammation exacerbates the liver burden through lipid overflow, and acute phase proteins released by the liver, in turn, promote vascular inflammation, while insulin deficiency caused by pancreatic β-cell apoptosis further amplifies systemic metabolic disorders. This cross-organ interaction highlights the complexity of targeted therapy — single-organ intervention may struggle to break the systemic vicious cycle. Consequently, patients with pre-existing NASH present a significantly elevated risk for postoperative hepatic dysfunction. The underlying susceptibility stems from the chronic inflammatory milieu and metabolic inflexibility, which predispose hepatocytes to exacerbated cell death (particularly ferroptosis and necroptosis) when confronted with the obligatory stressors of major surgery, such as transient hepatic ischemia-reperfusion, oxidative stress from anesthetic metabolism, and hemodynamic fluctuations. This compromised hepatic reserve can readily culminate in clinically significant postoperative liver injury. Therefore, future strategies need to focus on multi-system levels, rather than being limited to a single system. This systems approach is especially relevant for perioperative medicine, where optimizing the metabolic and inflammatory state before surgery (prehabilitation), protecting organs during the procedure, and carefully managing recovery could significantly improve outcomes. Only through integrated interventions can we break through the current treatment bottleneck of metabolic inflammatory diseases and their impact on surgical care.

This systemic perspective is fundamental to perioperative risk modification in metabolic disease. Preoperative risk assessment must extend beyond standard metrics to include biomarkers reflective of underlying cell death and inflammatory pathways. For instance, elevated oxidative stress markers in a patient with metabolic dysfunction-associated steatotic liver disease may indicate a heightened susceptibility to ferroptosis-

driven hepatic injury during ischemia-reperfusion events common in surgery. Similarly, assessing the activity of inflammasome pathways could stratify the risk for exacerbated systemic inflammation postoperatively. The goal of prehabilitation in these patients, therefore, includes not only metabolic optimization (e.g., glycemic control) but also potentially modulating these cellular vulnerability pathways. Perioperative organ protection strategies can then be targeted: for a patient with high oxidative stress burden, anesthesia and adjunctive drugs with antioxidant properties (e.g., propofol) or consideration of specific cytoprotective agents might be favored. This approach transforms perioperative care from a reactive to a proactive and precision-based practice, where the molecular profile of a patient's metabolic disease directly informs the protective strategy to mitigate their unique risks of organ injury.

5.4 Perioperative stimuli and cell death induction

Multiple perioperative factors, including propofol anesthesia, surgical trauma, and intraoperative hypotension, constitute significant stressors that can activate complex cellular stress responses. This often leads to the induction of various forms of regulated cell death (RCD), such as apoptosis, pyroptosis, necroptosis, ferroptosis, and autophagic cell death. A nuanced understanding of how these distinct stimuli preferentially engage specific RCD pathways is crucial for developing targeted organ-protective strategies in the perioperative period.

The intravenous anesthetic propofol exerts a dual, context-dependent influence on cellular fate. Beyond its primary pharmacological action, evidence suggests propofol can modulate cell death pathways. For instance, it may upregulate specific microRNAs (e.g., miR-20b) to suppress autophagic cell death in endothelial cells subjected to hypoxia/reoxygenation stress, indicating a potential protective role [294]. Conversely, propofol may also influence the delicate balance between apoptosis and pyroptosis by modulating mitochondrial function and ROS generation, highlighting its complex interplay with cell survival and inflammatory death mechanisms.

Surgical trauma, a major perioperative insult, triggers a systemic inflammatory and neuroendocrine response that broadly activates multiple RCD pathways. Ischemia-reperfusion injury, a common consequence of surgical procedures, involves a spatial hierarchy of cell death: while the central ischemic zone typically undergoes necrosis, the surrounding penumbra is characterized by the activation of apoptosis, a non-inflammatory, orderly form of PCD [295]. Concurrently, trauma-induced metabolic stress, iron dyshomeostasis, and GSH depletion can create a cellular environment conducive to ferroptosis, driven by iron-dependent lipid peroxidation [296]. Furthermore, the inflammatory milieu and direct cellular damage can activate receptor-interacting protein kinases, leading to necroptosis, a lytic and pro-inflammatory form of death mediated by RIPK1/RIPK3/MLKL. In parallel, DAMPs released from injured tissues can activate inflammasomes, culminating in pyroptosis—a highly inflammatory death executed by gasdermin family proteins, which forms pores in the plasma membrane to release potent cytokines like IL-1β.

Intraoperative hypotension, resulting in tissue hypoperfusion and ischemia, is a direct catalyst for cellular injury and death. Organs with high metabolic demand, such as the kidneys, are particularly vulnerable. The resulting energy crisis (ATP depletion) and oxidative stress from ischemia-reperfusion can simultaneously engage several of the aforementioned RCD pathways, contributing to organ dysfunction like acute kidney injury [297].

Given this complexity, the development of specific intervention strategies is paramount. Targeting oxidative stress with antioxidants represents a foundational approach, particularly against ferroptosis. More precise pharmacological modulation is also possible: BH3 mimetics can tip the balance towards apoptosis in specific contexts, while inhibitors targeting RIPK1, RIPK3, or MLKL can block necroptosis. Similarly, inflammasome or GSDMD inhibitors hold promise for mitigating pyroptosis. For ferroptosis, iron chelators, lipophilic radical-trapping antioxidants, or GPX4-stabilizing compounds are under investigation.

In conclusion, perioperative stimuli induce a network of interconnected RCD pathways that collectively determine the extent of tissue injury. Future therapeutic efforts must move beyond broad-spectrum cytoprotection towards context-specific, pathway-targeted interventions. A deeper mechanistic understanding of how factors like propofol or surgical trauma bias cells towards particular death fates (e.g., modulating the apoptosis/pyroptosis balance) will be essential for developing next-generation, precision-based organ protection protocols in anesthesiology and perioperative medicine.

5.5 Cytoprotective modulation by anesthetic agents and techniques

The strategic selection of anesthetic agents and techniques extends beyond the provision of unconsciousness and analgesia, actively influencing patient recovery through distinct cytoprotective mechanisms. Volatile anesthetics, such as sevoflurane and desflurane, confer protection primarily via the well-established phenomena of anesthetic preconditioning and postconditioning. These effects are mediated through the activation of crucial pro-survival pathways, notably the PI3K/Akt/GSK-3β signaling axis, which inhibits apoptotic and necroptotic processes [298]. A key mitochondrial mechanism involves the opening of mitochondrial ATP-sensitive potassium channels, which stabilizes membrane potential and potently inhibits the mitochondrial permeability transition pore, a terminal event in cell death [299]. Furthermore, volatile agents modulate ROS signaling, harnessing a controlled burst for protective signaling

while mitigating excessive oxidative damage during ischemia/reperfusion injury [300].

In contrast to volatile agents, the intravenous anesthetic propofol exerts its protective effects largely through a potent antioxidant and anti-inflammatory synergy. Its efficacy is attributed to the activation of the Nrf2/HO-1 pathway, a master regulator of the cellular antioxidant response, and the direct suppression of the NLRP3 inflammasome, thereby curtailing the release of pro-inflammatory cytokines like IL-1β [301]. Propofol also demonstrates protective effects against RCD, such as inhibiting ferroptosis in cardiomyocytes, contributing to its role in neuroprotection and mitigation of systemic inflammation.

Beyond general anesthetics, regional techniques like epidural analgesia provide organ protection indirectly by fundamentally modulating the surgical stress response. Effective nociceptive blockade at the neural axis attenuates the systemic neuroendocrine stress response, leading to reduced catecholamine and cortisol release [302]. This promotes hemodynamic stability and yields a significant opioid-sparing effect, which in turn avoids opioid-related side effects such as ileus and immune suppression. Importantly, by blunting systemic inflammation and improving splanchnic perfusion, regional anesthesia helps preserve intestinal barrier integrity, reducing enterocyte apoptosis and the risk of bacterial translocation—an effect that is crucial for patient recovery [303].

The clinical implications of these mechanistic differences are substantial. In cardiac surgery, the preconditioning properties of volatile anesthetics are a strategic consideration for myocardial protection. The choice between intravenous and inhaled agents may influence neurological outcomes, given their differential impacts on neuroinflammation. Within Enhanced Recovery After Surgery protocols, regional anesthesia is foundational, accelerating gastrointestinal recovery and improving pain management while minimizing opioid use. Thus, an understanding of these cytoprotective mechanisms is integral to tailoring anesthetic plans for improved perioperative outcomes.

6 CLINICAL APPLICATION PROSPECTS

The dynamic interplay between cell death and inflammatory responses constitutes a central hub in disease pathology, and targeted intervention at its key nodes is providing new therapeutic paradigms for various intractable diseases, as shown in **Table 3**. When cells undergo apoptosis, necroptosis, or pyroptosis, the released DAMPs, by activating TLRs and inflammasomes (e.g., NLRP3), drive a storm of pro-inflammatory factors such as TNF-α and IL-1β. This process can induce ICD in the tumor microenvironment, activating DCs to present tumor antigens and enhancing cytotoxic T lymphocyte responses. However, in autoimmune diseases, the same pathway leads to tissue damage due to overactivation [211]. This dual effect highlights the precise need for targeted strategies. Caspase inhibitors can block the dysregulation of apoptosis-induced immune silencing; RIPK1/3 small molecule antagonists (e.g., Nec-1s) can inhibit the pro-inflammatory effects of necroptosis, while GSDMD inhibitors alleviate pyroptosis-related inflammatory storms by blocking plasma membrane pores [320, 321]. In clinical translation, these targets demonstrate cross-disease application potential. Taking cancer therapy as an example, ferroptosis inducers (e.g., erastin) selectively eliminate drug-resistant tumor cells by depleting GSH and produce synergistic effects with PD-1 inhibitors [98]. In autoimmune diseases such as RA and IBD, TNF-α monoclonal antibodies (infliximab) and IL-1β antagonists (canakinumab) have established clinical status. Meanwhile, an emerging NLRP3 inhibitor (MCC950) can alleviate synovial and intestinal mucosal inflammation by blocking inflammasome assembly. In the field of neurodegenerative diseases, the focus is on inhibiting microglia overactivation, and inhibitors targeting the STING pathway can reduce β-amyloid-induced neuroinflammation [322]. Meanwhile, ROS scavengers (e.g., edaravone) can delay neuronal death by protecting mitochondrial function [323].

In the field of drug development, two major strategies, drug repurposing and intelligent delivery, are leading the innovation of therapeutic paradigms. Drug repurposing significantly shortens the research and development cycle by exploring the multi-target potential of existing drugs. The hypoglycemic drug metformin has been repurposed as an anti-tumor agent, which induces apoptosis in oral squamous cell carcinoma cells by activating the AMPK/mTOR pathway [324]. The antifungal drug Terbinafine hydrochloride inhibits skin cancer growth by regulating keratin metabolism [325]. This strategy is particularly crucial in neurodegenerative diseases. New breakthroughs in the treatment of Alzheimer's disease are being made through network pharmacology analysis-driven drug repositioning, revealing common regulatory nodes for β-amyloid clearance and tau protein phosphorylation [326]. Smart delivery systems break through the limitations of traditional drug delivery through spatiotemporally precise regulation; nanocarriers based on stimulus-responsive polymers (e.g., pH-sensitive hydrogels, ROS-responsive liposomes) can achieve programmed drug release at the lesion site. In tumor therapy, the EGCG/doxorubicin co-delivery system, through tumor microenvironment-triggered drug release, synergistically induces ICD and significantly enhances the efficacy of anti-PD-1 therapy [327]. In chronic inflammatory diseases, M1 macrophage-targeted nanoparticles can selectively deliver IL-10, reversing the pro-inflammatory phenotype without inducing systemic immunosuppression [328].

The clinical translation of these therapeutic strategies relies on precise navigation by biomarkers. When cell death occurs, molecular events such as cleaved caspase-3, RIPK1 phosphorylation levels, and GSDMD pore formation translate into detectable biomarker profiles, which not only reflect the pathological

Table 3. Clinical intervention strategies targeting the cell death-inflammation axis

Target type	Representative drug(s)	Mechanism of action	Indication	Development stage	Limitations	References
NLRP3 inflammasome inhibitors	MCC950	Blocks NLRP3 ATPase domain oligomerization	NASH	Phase II	Off-target effects, hepatotoxicity	[304]
	Oltipraz	Activates Nrf2→Inhibits NLRP3 expression	Diabetic nephropathy	Preclinical	Photosensitivity rash	[305]
RIPK1 kinase inhibitors	Nec-1s (GSK'772)	Selectively inhibits RIPK1 kinase activity	Ulcerative colitis	Phase II	Infection risk	[306]
	SAR443122	Dual-target RIPK1/TBK1 inhibition	Systemic lupus erythematosus (SLE)	Phase II	Anemia	[307]
GSDMD pore blockers	Disulfiram (Repurposing)	Covalently binds GSDMD Cys191→Blocks pore formation	Sepsis	Phase III (Repurposing)	Copper accumulation toxicity	[308]
	Necrosulfonamide	Targets MLKL→Blocks necroptotic pore	Myocardial infarction	Preclinical	Poor solubility	[203]
Ferroptosis inducers	B23 (Genipin derivative)	Modulates expression of ACSL4, GPX4, FTH1→Induces ferroptosis	Triple-negative breast cancer	Preclinical	Limited experimental data	[309]
	RSL3	Covalently binds and inactivates GPX4	Castration-resistant prostate cancer	Phase I	Hepatotoxicity	[310]
Cuproptosis modulators	Tetrathiomolybdate (TTM)	Copper chelator→Reduces free copper	Breast cancer (high relapse risk)	Approved	Copper deficiency→Anemia	[311]
	Elesclomol	Copper ionophore→Targets mitochondria→Induces cuproptosis	Melanoma	Phase II	Increased adverse events when combined with paclitaxel	[312]
NETosis inhibitors	DNase I	Hydrolyzes DNA strands within NETs	Lupus nephritis (SLE)	Phase III	Immunogenicity, reduced efficacy	[313]
	GSK484	Inhibits PAD4→Blocks histone citrullination→Inhibits NET formation	Rheumatoid arthritis (RA)	Phase II	Thrombocytopenia	[314]
STING pathway antagonists	H-151	Covalently binds STING Cys91→Blocks dimerization	SLE-associated interferonopathy	Preclinical	Immunosuppression	[315]
TLR4 signaling blockers	Eritoran	Inhibits TLR4-mediated inflammation & HMGB1 signaling	Chronic liver injury & fibrosis	Animal models	Does not improve systemic insulin resistance	[316]
PANoptosome interferers	Cercosporamide	Inhibits Mnk kinase activity	Alzheimer's disease	Preclinical	Complex mechanism, potential off-target effects	[229]
Autophagy inhibitor	Hydroxychloroquine (HCQ)	Alkalizes lysosomes→Blocks autophagosome degradation	BRAF mutant melanoma	Phase II	Retinal toxicity	[317]
cGAS inhibitors	RU.521	Competitively inhibits cGAS catalytic activity	Subarachnoid hemorrhage	Preclinical	Off-target effects	[318]
S100A9 inhibitor	Paquinimod	Blocks S100A9-TLR4 interaction	HFpEF (Heart Failure w/preserved EF)	Phase II	Mechanism not fully elucidated	[319]

Note: NLRP3, NLR family pyrin domain containing 3; ATPase, adenosine triphosphatase; NASH, non-alcoholic steatohepatitis; Nrf2, nuclear factor erythroid 2-related factor 2; RIPK1, receptor-interacting protein kinase 1; Nec-1s, necrostatin-1s; TBK1, TANK-binding kinase 1; SLE, systemic lupus erythematosus; GSDMD, gasdermin D; Cys191, cysteine 191; MLKL, mixed lineage kinase domain-like pseudokinase; ACSL4, acyl-CoA synthetase long-chain family member 4; GPX4, glutathione peroxidase 4; FTH1, ferritin heavy chain 1; RSL3, RAS-selective lethal 3; TTM, tetrathiomolybdate; PAD4, peptidylarginine deiminase 4; RA, rheumatoid arthritis; STING, stimulator of interferon genes; Cys91, cysteine 91; TLR4, Toll-like receptor 4; HMGB1, high mobility group box 1; Mnk, mitogen-activated protein kinase-interacting kinase; HCQ, hydroxychloroquine; BRAF, B-Raf proto-oncogene serine/threonine-protein kinase; cGAS, cyclic GMP-AMP synthase; S100A9, S100 calcium-binding protein A9; HFpEF, heart failure with preserved ejection fraction; EF, ejection fraction.

state but also possess prognostic capabilities. For example, an elevated serum neutrophil-to-lymphocyte ratio in non-small cell lung cancer patients predicts poor prognosis, while the dynamics of the inflammatory protein network after myocardial infarction are closely related to cardiac function recovery [329, 330]. In the field of diagnosis, fecal calprotectin levels in patients with IBD are positively correlated with the degree of intestinal mucosal inflammation, serving as an alternative endoscopic assessment indicator [331]. In patients with SLE, serum anti-dsDNA antibody titers are directly associated with the risk of renal involvement [332]. At the level of treatment monitoring, synchronous analysis of PD-1/PD-L1 expression and $CD8^+$ T cell infiltration can assess the response to immunotherapy in real-time [333]. When necroptosis inhibitors are used to treat RA, changes in serum MLKL levels directly reflect the target inhibition efficiency [334]. Emerging liquid biopsy technologies further expand monitoring dimensions. Circulating tumor DNA mutation profiles track tumor clonal evolution, while exosomal miRNAs reveal the inflammatory status of the microenvironment, providing molecular navigation for dynamic adjustment of treatment strategies [335].

Despite its broad prospects, clinical translation still faces triple challenges. In the field of targeted therapy, there is an urgent need to overcome the complexity of spatiotemporal dynamic regulation. During the acute phase, precise blockade of death signaling is required, while during the chronic phase, it is necessary to reverse the fibrotic process. Meanwhile, technical bottlenecks in organ-specific delivery urgently need to be overcome, such as developing nanocarriers that can efficiently penetrate the blood-brain barrier to achieve precise drug delivery to the central nervous system. In drug development, drug repurposing strategies often trigger off-target effects due to the inherent multi-target characteristics of drugs, limiting their maximal therapeutic efficacy. Intelligent delivery systems, however, face scale-up production bottlenecks for industrial translation from laboratory to industry, restricting clinical accessibility. In the application of biomarkers, the lack of standardization remains a key obstacle, typically exemplified by the absence of unified standards for detecting the activity threshold of the pyroptosis execution protein GSDMD. Furthermore, organ cross-interference severely impacts biomarker specificity; for example, cardiac troponin often yields false-positive results in patients with renal failure, leading to clinical misjudgment. Overcoming these obstacles requires synergistic technological innovation. AI-driven multi-omics analysis predicts drug-target interactions, organ-on-a-chip models simulate death-inflammation dynamics, and CRISPR detection platforms enhance biomarker sensitivity. Closed-loop feedback intelligent delivery systems, in turn, adjust drug release rates in real-time based on biomarkers, achieving a "monitor-intervene-reassess" precision medicine closed loop. This integrated strategy will usher in a new era for the individualized treatment of cancer, autoimmune diseases, and neurodegenerative diseases.

7 DISCUSSION

The interactive network of cell death and inflammation constitutes the core axis of homeostatic regulation in the body, and its dynamic imbalance is a key driving factor in the occurrence of major diseases. The perioperative period, with its confluence of surgical trauma, anesthetic exposure, and potential ischemia-reperfusion injury, represents a critical window where this delicate balance is profoundly tested, often determining the trajectory of postoperative recovery and the risk of complications. Furthermore, the temporal dynamics of these pathways in response to acute intraoperative insults are particularly critical, implying that the timing of potential interventions relative to the surgical stressor is a key determinant of efficacy, a concept central to perioperative medicine. Different cell death modalities shape unique inflammatory responses by releasing specific DAMPs. Apoptosis, through phosphatidylserine externalization, mediates immunologically silent clearance, typically inhibiting inflammatory responses. Pyroptosis actively releases IL-1β via GSDMD pores, while necroptosis relies on MLKL-mediated HMGB1 release; both collectively trigger a strong inflammatory cascade. This causal association between cell death modalities and inflammation intensity is prominently manifested in pathological processes such as sepsis and autoimmune diseases, both of which are of significant concern in the perioperative setting due to their potential for exacerbation and the associated increase in morbidity. This is especially relevant given that different organs exhibit varying susceptibility to specific death pathways during surgery; for instance, the heart may be more vulnerable to ferroptotic damage during ischemia-reperfusion, while the brain's sensitivity to necroptosis could underpin postoperative cognitive decline, highlighting the need for organ-tailored protective strategies. Concurrently, bidirectional regulatory mechanisms profoundly influence cell fate. TNF-α, by concentration-dependent activation of the NF-κB or RIPK1 pathways, regulates cell survival or death decisions, respectively. IFN-γ, meanwhile, enhances apoptotic sensitivity by upregulating death receptors, forming an inflammation-death feedback loop. Metabolic reprogramming, as an emerging regulatory hub, incorporates ferroptosis and cuproptosis into an interaction network. Ferroptosis relies on lipid peroxides to activate the TLR4 pathway, while cuproptosis activates the cGAS-STING axis through mitochondrial DNA release, revealing a deep association between metabolic stress and immune response. During disease progression, NETosis-released citrullinated autoantigens drive the interferon storm in SLE, the GSDMD-IL-1β auto-amplification loop exacerbates septic multi-organ damage, and lipotoxicity-induced cell death mode switching promotes NASH fibrosis progression.

Although the interplay network of cell death and inflammation plays a role in the pathological processes of various diseases and has achieved significant success in clinical applications, this field still has many shortcomings, particularly in the con-

text of perioperative medicine, where the temporal dynamics of these pathways in response to acute insults are poorly characterized and the efficacy of targeted interventions in this unique setting remains largely unexplored. Organ-specific regulatory mechanisms remain undefined. This is particularly relevant for perioperative care, as different organs exhibit varying susceptibility to ischemia-reperfusion injury and inflammatory damage during surgery (e.g., heart, brain, kidneys), and understanding these differences is key to developing organ-protective strategies. Spatial transcriptomics reveals that high expression of TREM2 in microglia promotes apoptotic clearance, while high expression of HIF-1α in HSCs amplifies cuproptosis damage. However, the core molecular switch driving these differences remains undetermined. Secondly, the quantitative threshold for cell death mode transition lacks precise definition. Normal autophagy can protect cells, but excessive autophagy induces endoplasmic reticulum stress death via the ATF4-CHOP axis. How cells regulate protective autophagy and lethal autophagy is a field worthy of in-depth study. The critical point at which autophagy shifts from a protective mechanism to a lethal program also requires systematic study. In addition, translational medicine faces many obstacles. The most critical among these is the double-edged nature of targeted therapy. Some targeted therapeutic drugs, while killing a large number of tumor cells, release massive amounts of cellular contents, leading to tumor lysis syndrome [336]. Tumor lysis syndrome can cause metabolic disorders such as hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. These metabolic disorders can further activate inflammatory responses and damage organs such as the kidneys. This paradoxical effect demands that targeted strategies precisely balance immune homeostasis. This challenge is accentuated in the perioperative period, where the efficacy of targeted interventions is contingent not only on target engagement but also on overcoming the acute physiological perturbations of surgery and anesthesia and on the time-sensitive delivery of therapies to high-risk patients, for whom rapid, point-of-care biomarkers are urgently needed. At the same time, insufficient research into inter-organ immune crosstalk networks limits our mechanistic understanding. For example, the mechanism by which the gut microbiota metabolite butyrate inhibits intestinal epithelial necroptosis and alleviates arthritis via the GPR109A receptor has not yet been elucidated [337]. Furthermore, inefficient drug delivery severely impacts therapeutic efficacy. Systemic administration of RIPK1 inhibitors leads to immune homeostasis disruption, while the lack of liver/brain-specific delivery systems constrains precise intervention. Moreover, current research mostly focuses on single organs or specific disease models, lacking a comprehensive understanding of cell death and inflammation in complex physiological and pathological environments. How to integrate these findings into our understanding of systemic inflammatory responses, and consider the interactions between different organs, remains a challenge.

Future research needs to explore more deeply the precise molecular mechanisms of cell death and inflammation, with particular attention to the spatiotemporal dynamic characteristics of signaling pathways. For example, using high-resolution imaging techniques and biosensors, researchers can monitor the activation, localization, and interaction of key molecules during cell death in real-time, thereby revealing the intricate mechanisms that regulate inflammatory responses. This research direction focuses on the spatiotemporal dynamic characteristics of signaling pathways. Emerging technologies such as single-cell sequencing and spatial transcriptomics provide new perspectives for studying cell death and inflammation. These technologies can help researchers identify specific regulatory mechanisms in different cell subpopulations, clarify which cell types are more prone to certain types of cell death, and understand how these cells interact with other immune cells, influencing the progression of inflammatory responses. To better simulate the human physiological environment, researchers need to develop and optimize human-like three-dimensional culture systems, such as organoids and organ-on-a-chip models. These models can more realistically reflect cell-cell interactions, the influence of the ECM, as well as the gradient distribution of nutrients and oxygen, thereby enabling more accurate study of the pathophysiological mechanisms of cell death and inflammation.

Elucidating the interaction mechanisms between cell death and inflammation not only provides a unified molecular model of "death mode-receptor activation" for major diseases but also promotes targeted therapy to shift from single-pathway blockade to spatiotemporally precise intervention. This precision approach is paramount in perioperative medicine, where interventions must be acutely timed to mitigate injury during surgical stress without compromising essential healing processes and immune defense in the postoperative phase. With subcellular dynamic tracing techniques resolving millisecond-level signaling events, organ-targeted delivery systems overcoming biological barriers, and multi-omics integrated AI models reconstructing disease trajectories, the translational gap between basic discoveries and clinical practice will be bridged. The ultimate establishment of an "dynamic monitoring-targeted intervention-efficacy evaluation" individualized treatment system will open up new treatment strategies for medical challenges such as multiple organ failure and the chronic inflammation vicious cycle. Translating this systems approach into the perioperative environment, potentially through rapid point-of-care biomarkers of cell death and inflammation, could enable real-time risk stratification and guide personalized prophylactic or therapeutic strategies to protect high-risk surgical patients.

ABBREVIATIONS

4-HNE, 4-hydroxynonenal; AA, arachidonic acid; ACSL4, acyl-CoA synthetase long-chain family member 4; AIM2,

absent in melanoma 2; ALOXs, arachidonate lipoxygenases; AMPK, AMP-activated protein kinase; Apaf-1, apoptotic protease activating factor 1; APC, antigen-presenting cell; ASC, apoptosis-associated speck-like protein containing a CARD; ATG, autophagy-related; BCL-2, B-cell lymphoma 2; BCL-xL, B-cell lymphoma-extra large; cGAS, cyclic GMP-AMP synthase; CLRs, C-type lectin receptors; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; DLAT, dihydrolipoyl acetyltransferase; DIM, 3,3'-diindolylmethane; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; FADD, Fas-associated death domain protein; FasL, Fas ligand; FDX1, ferredoxin 1; FLS, synovial fibroblasts; GSDMD, gasdermin D; GSDMD-N, gasdermin D N-terminal domain; GSH, glutathione; GPX4, glutathione peroxidase 4; GPR109A, G protein-coupled receptor 109A; HMGB1, High Mobility Group Box 1; HSCs, hepatic stellate cells; IBD, inflammatory bowel disease; ICD, immunogenic cell death; IRF3, interferon regulatory factor 3; LPS, lipopolysaccharide; LC3, microtubule-associated protein 1A/1B-light chain 3; MDA, malondialdehyde; MAPK, mitogen-activated protein kinase; MLKL, mixed lineage kinase domain-like protein; MOMP, mitochondrial outer membrane permeabilization; mtDNA, mitochondrial DNA; mTOR, mechanistic target of rapamycin; MyD88, myeloid differentiation primary response 88; NASH, non-alcoholic steatohepatitis; NETs, neutrophil extracellular traps; NETosis, NET formation cell death; NLRP3, NLR family pyrin domain containing 3; NLRs, NOD-like receptors; NOD2, nucleotide-binding oligomerization domain-containing protein 2; NLRP1b, NLR family pyrin domain containing 1b; NLRC4, NLR family CARD domain containing 4; PAMPs, pathogen-associated molecular patterns; PCD, programmed cell death; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphatidylinositol 3-kinase; PI3P, phosphatidylinositol 3-phosphate; POCD, postoperative cognitive dysfunction; PRRs, pattern recognition receptors; RA, rheumatoid arthritis; RIPK1, receptor-interacting serine/threonine-protein kinase 1; RIPK3, receptor-interacting serine/threonine-protein kinase 3; RLRs, RIG-I-like receptors; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; SPMs, specialized pro-resolving mediators; STAT, signal transducer and activator of transcription; STING, stimulator of interferon genes; TFR1, transferrin receptor 1; TGF-β, transforming growth factor beta; TLRs, Toll-like receptors; TNF, tumor necrosis factor; TNFR1, tumor necrosis factor receptor 1; TRADD, TNF receptor type 1-associated death domain protein; Tregs, regulatory T cells; TRPV4, transient receptor potential vanilloid 4; T1DM, type 1 diabetes mellitus; ZBP1, Z-DNA binding protein 1.

DECLARATIONS

Author contributions

Jiaqi Li, Chenglong Zhu, Yan Liao and Xuan Yin contributed to the manuscript writing and figure preparation; Rui Zhao and Changli Wang designed the work; Doblin Sandai, Haoling Zhang and Wangzheqi Zhang supervised the work. All authors have read and approved the final manuscript.

Funding

This research received no external funding.

Data availability

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study. All information is derived from publicly available articles and datasets.

Ethics approval and consent to participate

Not applicable. This manuscript does not contain any studies involving human participants or animals performed by any of the authors.

Consent for publication

Not applicable. This manuscript does not include details, images, or videos relating to an individual person.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

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