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REVIEW

Crosstalk Between Cell Death and the cGAS-STING Pathway in Sepsis-Associated Acute Lung Injury

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Abstract: Sepsis-associated acute lung injury (ALI) is a complex pathological condition characterized by dysregulated inflammatory responses and the activation of various cell death mechanisms. This review examines the interplay between cell death pathways and the cGAS-STING signaling pathway in sepsis-associated ALI. The cGAS-STING pathway, which recognizes pathogen-derived DNA to trigger innate immune responses, can exacerbate lung injury when dysregulated. Recent studies have revealed that apoptosis, pyroptosis, necroptosis, autophagy, ferroptosis, NETosis, and PANoptosis are all intricately linked to the cGAS-STING pathway. These cell death mechanisms interact synergistically to amplify inflammation and tissue damage. Targeting the cGAS-STING pathway has been shown to reduce both inflammation and cell death in sepsis-associated ALI. For instance, inhibiting the stimulator of interferon genes (STING) pathway can mitigate ferroptosis and inflammation in macrophages, suggesting its potential as a therapeutic target. Furthermore, exosome-based therapies that modulate immune responses and promote tissue repair are emerging as promising strategies for treating ALI. However, further research is needed to fully elucidate the specific mechanisms through which the cGAS-STING pathway regulates cell death and inflammation in ALI. Additionally, exploring combination therapies that integrate STING inhibitors with other treatments, such as anti-inflammatory agents, may offer improved clinical outcomes in sepsis-associated ALI.

Keywords: sepsis, ALI, cell death, cGAS-STING pathway, inflammatory response, therapeutic targets

Introduction

Sepsis is characterized by a dysregulated host response to infection, which can lead to life-threatening organ dysfunction.[1] It is a major risk factor for ALI, with the lungs being particularly vulnerable during the multiorgan dysfunction phase.[2] Over 40% of sepsis patients develop acute respiratory distress syndrome (ARDS).[3] During sepsis, damage to the lung capillary endothelium increases vascular permeability, allowing protein-rich exudates to accumulate. This disrupts the lung epithelial barrier, filling the alveoli and impairing gas exchange, which leads to severe hypoxemia hallmarks of ALI.[4] An epidemiological study conducted in China found that the 90-day mortality rate for 2322 sepsis patients across 44 intensive care units was 35.5%, with 68.2% of these patients also suffering from ARDS.[5] (Terminology Note: While recent clinical guidelines favor "ARDS" for severe human syndromes characterized by acute hypoxemic respiratory failure, we retain "ALI" as an umbrella term encompassing the pathophysiological continuum from initial injury to organ failure. This aligns with preclinical literature and acknowledges that the molecular mechanisms discussed herein underpin both ALI and ARDS). Despite the high prevalence and mortality of sepsis-induced ALI, current clinical management primarily relies on supportive therapies, including respiratory support (non-invasive/invasive/prone ventilation) and extracorporeal membrane oxygenation (ECMO), while focusing on treating the underlying infection or disease. However, this approach imposes a substantial economic burden on society.[6] Moreover,

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the pathophysiology and molecular mechanisms of sepsis-associated ALI remain poorly understood, and effective pharmacological treatments are limited.[7] Additionally, current clinical approaches remain predominantly supportive rather than mechanism-targeted, while persistent knowledge gaps regarding molecular drivers, particularly how distinct cell death modalities interact with immune pathways like STING, hinder therapeutic development. Therefore, it is critical to investigate the underlying mechanisms of sepsis-associated ALI and explore potential therapeutic strategies to improve patient outcomes.

Apoptosis, necrosis, autophagic cell death, and other forms of cell death have been implicated in the pathogenesis of ALI.[8–10] However, the inflammatory responses and mediator release associated with these processes alone do not fully account for the complex inflammatory mechanisms underlying ALI. In recent years, novel forms of programmed cell death such as ferroptosis, necroptosis, and NETosis have emerged as promising research avenues in the study of ALI.[11–13]

The cGAS-STING signaling pathway plays a crucial role in the innate immune response by recognizing pathogenic DNA and initiating antiviral and antimicrobial defenses (Figure 1). This pathway involves cyclic GMP-AMP synthetase (cGAS), stimulator of interferon genes (STING), and various downstream signaling adapters. Upon detecting intracellular pathogenic DNA, cGAS catalyzes the production of cyclic GMP-AMP (cGAMP), which activates STING and triggers a signaling cascade that leads to the production of type I interferons and pro-inflammatory cytokines, initiating an immune response.[14] Dysregulated activation of the STING pathway can exacerbate lung injury by promoting excessive cell death. In summary, the interaction between cell death mechanisms and the STING pathway in sepsis-induced acute lung injury is a complex process, involving multiple cell death modalities and the regulation of inflammatory responses. Future research should focus on further elucidating the molecular interactions within this pathway to identify novel therapeutic targets and strategies for the clinical management of sepsis.

Crosstalk Between Cell Death and the cGAS-STING Pathway

Recent studies have shown that the interaction between cell death and the cGAS-STING pathway can regulate the occurrence and progression of sepsis-associated ALI. Table 1 list the key molecules and pathway interactions of cell death mechanisms in sepsis-associated ALI.

Apoptosis

Apoptosis is a self-defense mechanism of the body, initiated through three pathways: death receptors, mitochondria, and granzyme pathways, ultimately activating caspases. In the mitochondrial pathway, following apoptotic stimuli, the Bax/Bak complex inserts into the outer mitochondrial membrane, leading to the release of cytochrome C, which binds to Apaf-1 and activates Caspase-9. This, in turn, triggers a caspase cascade, inducing apoptosis.[22–24] The death receptor pathway is initiated by extracellular “death ligands” binding to “death receptors”, activating Caspase-8. Caspase-8 then cleaves BH3 Interacting Domain Death Agonist (BID), which collaborates with the mitochondrial pathway to activate Caspase-3.[25] The granzyme pathway is mediated by cytotoxic granule components (such as Perforin and Granzyme B) released by cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells.[26,27] In ARDS patients and ALI animal models, significant activation of apoptosis can be observed in alveolar epithelial cells, leading to dysfunction of alveolar, airway epithelial, and endothelial cells.[77–79] Inhibiting apoptosis can reduce lung injury.[80] Additionally, apoptosis may lead to microvascular dysfunction, organ failure,[81,82] and secondary infections or immune suppression caused by immune cell apoptosis, which adversely affects prognosis.[83]

Mitochondrial DNA (mtDNA) plays a crucial role in the interaction between the STING signaling pathway and apoptosis (Figure 2).[30,31] Mitochondrial apoptosis is regulated by the Bcl-2 family, with the Bax/Bak channel formation increasing the mitochondrial outer membrane permeability (MOMP).[15,16] The released mtDNA is detected by the cGAS/STING pathway, which activates the STING-TBK1-IRF3 pathway, leading to Caspase-3 activation and inducing apoptosis.[17] Interferon regulatory factor 3 (IRF3) regulates cell death in sepsis-associated ALI. For instance, inhibiting the stimulator of interferon genes (can also bind to Bak/Bax, releasing mitochondrial cytochrome C,[18,19] which assembles the Apaf1-Caspase-9 apoptosome, activating Caspase-3/7 to mediate apoptosis. The ER stress induced by STING pathway activation can also lead to mitochondrial damage and cell death through various mechanisms.[20,21]

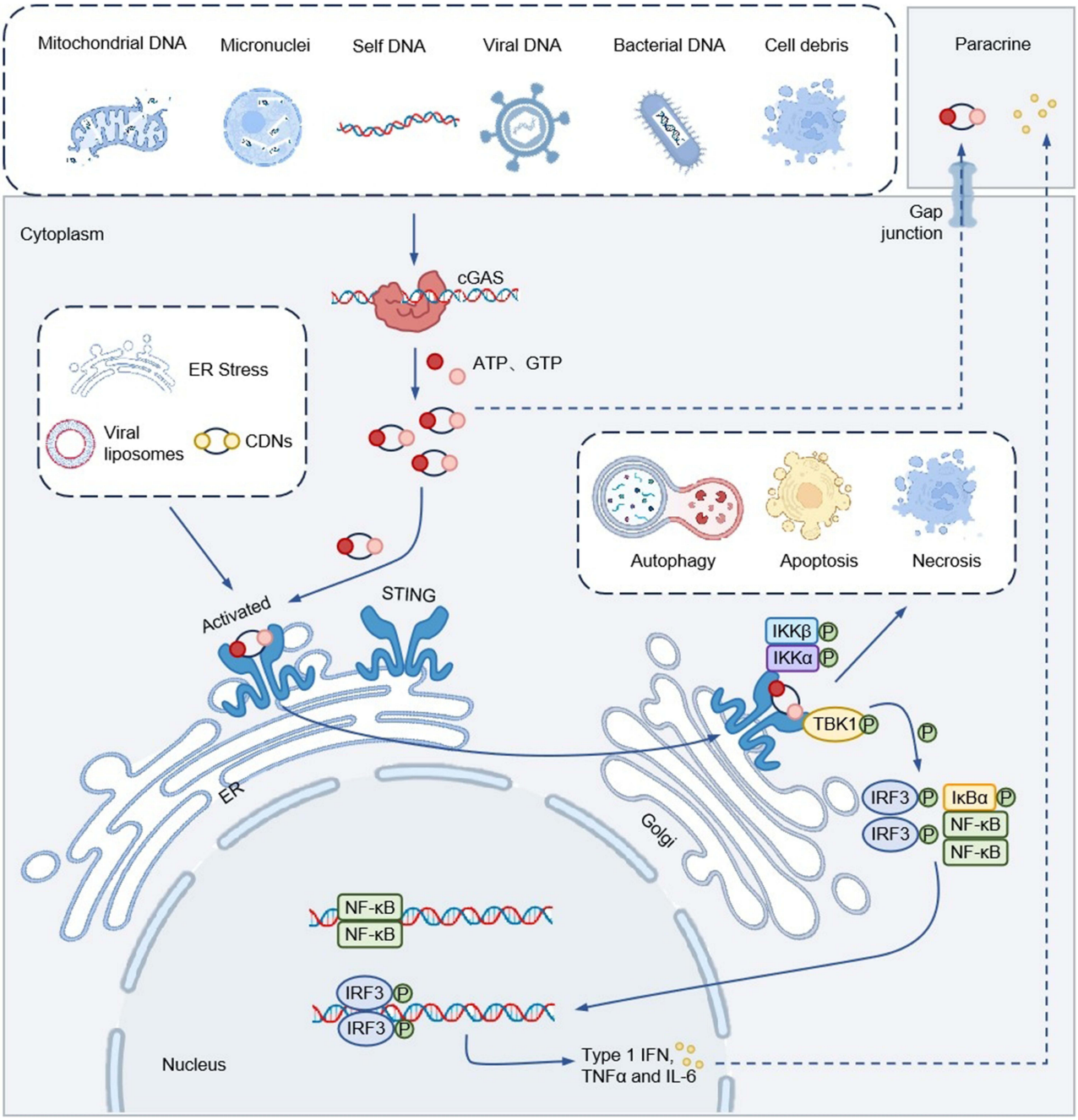

Figure 1 Schematic of the cGAS-STING pathway and its physiological roles. Cytoplasmic DNA from various sources, including mitochondrial DNA, micronuclei, self DNA, viral DNA, bacterial DNA, and cellular debris, is sensed by cGAS. This interaction leads to the production of cGAMP, which activates the STING receptor. Subsequently, STING initiates a signaling cascade involving TBK1, leading to the phosphorylation of IRF3 and NF-κB. These events culminate in the transcriptional activation of type I interferons (IFNs), TNF-α, and IL-6. Additionally, the pathway intersects with cellular stress responses, such as ER stress and viral liposomes, influencing autophagy, apoptosis, and necrosis. This intricate network highlights the critical role of the cGAS-STING pathway in antiviral immunity and cellular homeostasis.

Additionally, caspases may inhibit the production of interferons (IFNs) during the Bak/Bax-mediated apoptosis process.[28,29] The mechanisms of negative regulation in the cGAS-cGAMP-STING pathway remain unclear, but they may involve gene expression suppression, cleavage and inactivation of components in the IFN production pathway, and caspase-mediated degradation of mtDNA, disrupting its interaction with cGAS and preventing pathway activation and downstream IFN effects.[28] In sepsis-induced acute lung injury, the cGAS-STING signaling pathway is widely activated, with a complex interaction with apoptosis, but the specific mechanisms still require further investigation.

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Table 1 Key Molecules and Pathway Interactions of Cell Death Mechanisms in Sepsis-Associated ALI

Cell Death Type	Key Molecule/ Pathway	Function/Role	Interaction with cGAS-STING Pathway	References
Apoptosis	Bax/Bak	Forms channels to increase mitochondrial outer membrane permeability (MOMP)	MOMP → mtDNA release → cGAS activation → STING-TBK1-IRF3 axis → Caspase-3 activation → apoptosis	[15–17]
	Cytochrome c	Binds Apaf-1 to form apoptosome	STING activation → ER stress → Bak-dependent cytochrome c release → Caspase-9 activation → apoptosis	[18–21]
	Caspase-9	Initiator caspase; triggers caspase cascade	Cytochrome c/Apaf-1 → Caspase-9 activation → Caspase-3/7 cleavage → apoptosis	[22–24]
	Caspase-8	Activated by death ligand-receptor binding	Cleaves Bid → synergizes with mitochondrial pathway → Caspase-3 activation → apoptosis	[25]
	Granzyme B	Released by CTLs/NK cells; directly activates caspases	Induces apoptosis → mtDNA release → activates cGAS-STING	[26,27]
	Caspase-3	Executioner caspase	1. Pro-apoptotic: cGAS-STING → Caspase-3 activation 2. Negative feedback: Cleaves IRF3/STING → suppresses IFN production	[17,28,29]
	mtDNA	Damage-associated molecular pattern (DAMP) released during mitochondrial damage	Central bridge: Apoptosis → mtDNA release → cGAS sensing → 1. Pro-apoptosis (Caspase-3) 2. Inflammation (IFN) 3. ER stress → mitochondrial damage	[15–17,30,31]
	IRF3	Downstream transcription factor of STING	1. Pro-apoptotic: Binds Bak/Bax → cytochrome c release 2. Negative regulation: Cleaved by Caspase-3 → inhibits IFN signaling	[18,19,28]

Pyroptosis	NLRP3	Inflammasome sensor	1. STING recruits NLRP3 to ER membrane → promotes deubiquitination 2. STING proton leakage activates NLRP3	[32,33]
	Caspase-1	Cleaves GSDMD & pro-cytokines	1. STING → lysosomal cell death → K^+ efflux → NLRP3 inflammasome → Caspase-1 activation 2. Negative feedback: Cleaves cGAS → inhibits IFN production	[34,35]
	GSDMD	Pore-forming executioner	cGAS-STING-NLRP3 axis → Caspase-1-mediated cleavage → membrane rupture	[36,37]
	AIM2	Cytosolic DNA-sensing inflammasome	STING → IRF1 → GBP expression → AIM2 inflammasome activation → Caspase-1 recruitment	[38]
	Caspase-4/5/11	Non-classical pyroptosis execution	Direct LPS recognition → GSDMD cleavage Francisella infection: Downstream of STING-AIM2 axis	[38,39]
	NLRC3/NLRP4	Inflammasome regulators	Negative regulation: 1. NLRC3 binds STING → blocks translocation/TBK1 binding 2. NLRP4-DTX4 degrades TBK1	[40,41]
Necroptosis	RIPK3	Core necroptosis kinase; phosphorylates MLKL	1. STING → IFN-I → upregulates RIPK3 → disrupts redox homeostasis 2. RIPK3 inhibits STING autophagy → sustains STING signaling 3. mtDNA → STING → enhances RIPK3 phosphorylation (via TNF-α/PUMA)	[42–44]
	MLKL	Executioner; forms membrane pores	1. STING maintains constitutive MLKL expression 2. MLKL oligomerization promotes STING phosphorylation (pre-TBK1 recruitment) 3. Blocking MLKL oligomerization → reduces STING activation	[44,45]
	TNF-α/IFN-I	Pro-inflammatory cytokines	STING activation → induces TNF-α/IFN-I → drives necroptosis initiation 1. IFN-I upregulates RIPK3/Pgam5 2. TNF-α activates RIPK1-RIPK3 axis	[42,43,45–47]
	PUMA/DAI(Zbp1)	mtDNA release and cytosolic DNA sensing	PUMA → mtDNA release → activates DAI/Zbp1 & STING → enhances RIPK3/MLKL phosphorylation (positive feedback)	[48]

(*Continued*)

Table 1 (Continued).

Cell Death Type	Key Molecule/ Pathway	Function/Role	Interaction with cGAS-STING Pathway	References
Autophagy	LC3-II	Autophagosome membrane marker	STING activation → ATG16L1/V-ATPase-dependent LC3 lipidation (pro-autophagic)	[49]
	p62/SQSTM1	Selective autophagy adaptor	Degrades STING via selective autophagy → suppresses cGAS-STING signaling	[50]
	ULK1	Autophagy initiation kinase	STING hyperactivation → ULK1 S757 phosphorylation → inhibits autophagy initiation	[51]
	Beclin-1	PI3K complex component	1. Binds cGAS → inhibits cGAMP production 2. Releases Rubicon → activates PI3K (pro-autophagic)	[52]
	mTOR	Autophagy suppressor	1. STING-PERK → inactivates mTOR → induces ER-phagy 2. STING activation → enhances mTOR → inhibits autophagy (context-dependent)	[53,54]
	AMPK	Autophagy activator	Phosphorylates STING S366 → promotes STING degradation → negative feedback	[55]
	STX17	Autophagosome-lysosome fusion factor	Nutrient-rich: STING binds STX17 → inhibits fusion Starvation: STX17 released → promotes fusion	[56]
Ferroptosis	NCOA4	Ferritinophagy receptor	1. STING binds NCOA4 → promotes ferritin degradation → iron release → lipid peroxidation 2. Reduces NCOA4 nuclear localization → indirectly promotes ferroptosis	[57]
	GPX4	Anti-lipid peroxidation enzyme	1. STING inhibits System Xc^- → reduces GSH synthesis → GPX4 inactivation 2. GPX4 maintains redox homeostasis → promotes STING dimer stability	[58]
	FPN1	Iron exporter	STING activation → degrades FPN1 → disrupts iron homeostasis → promotes ferroptosis	[59,60]
	System Xc^-	Cystine/glutamate antiporter	STING inhibits System Xc^- → reduces GSH → weakens antioxidant capacity	[58,61]
	ACSL4	PUFA esterification enzyme	STING → regulates ACSL4 activity → increases lipid peroxide generation	[62]
	Exosomes (Ficolin B)	Macrophage-derived mediators	Activate cGAS-STING → ↑ MDA/iron accumulation + ↓ GSH → autophagy-dependent ferroptosis	[63]

NETosis	PAD4	Histone citrullination enzyme	1. NETs → activate cGAS-STING → upregulate PAD4 → chromatin decondensation 2. ROS → activate PAD4 → NET formation	[64]
	GSDMD	Pore-forming execution protein	1. mtDNA-cGAS-STING axis → GSDMD cleavage → mtDNA release → NET formation 2. Caspase-11 → cleaves GSDMD → membrane rupture	[65–68]
	NETs	Neutrophil extracellular traps	1. Activate cGAS-STING → lung epithelial damage 2. DNase I degrades NETs → reduces cGAS-STING activation 3. NETs-STING-TF axis → TLR2 activation → TF expression → inflammation-coagulation imbalance	[69,70]
	TLR2	Pattern recognition receptor	Mediates NETs-induced STING activation → tissue factor (TF) expression → amplifies inflammation/coagulation	[70]
	mtDNA	Mitochondrial damage signal	1. GSDMD cleavage → mtDNA release → activates cGAS-STING → NET formation 2. Forms positive feedback loop with NETosis	[68]
	Platelet STING	Modulates thrombosis	1. STING-STXBP2 interaction → promotes platelet activation 2. P-selectin → neutrophil-platelet aggregation → NETosis	[71]
PANoptosis	ZBP1	PANoptosome sensor	STING activation → ZBP1-dependent assembly of RIPK3/CASPB complex → PANoptosome formation	[72,73]
	Caspase-8	Apoptosis-pyroptosis crossover	STING-TBK1 axis → activates Caspase-8 → cleaves GSDMD/GSDME → membrane rupture	[74]
	PANoptosome	Integrated death complex	STING promotes assembly of Caspase-8/RIPK3/ASC complex → triggers: 1. MLKL phosphorylation (necroptosis) 2. Caspase-3 cleavage (apoptosis) 3. GSDME cleavage (pyroptosis)	[75]
	mtDNA	Mitochondrial DAMP	1. Bacterial/heme stress → mtDNA release → activates cGAS-STING 2. Exacerbates PANoptosis in Kupffer cells	[76]
	GSDMD/GSDME	Pore-forming executioners	Cleaved by Caspase-8 (STING-activated) → membrane disruption → inflammatory death	[74,75]

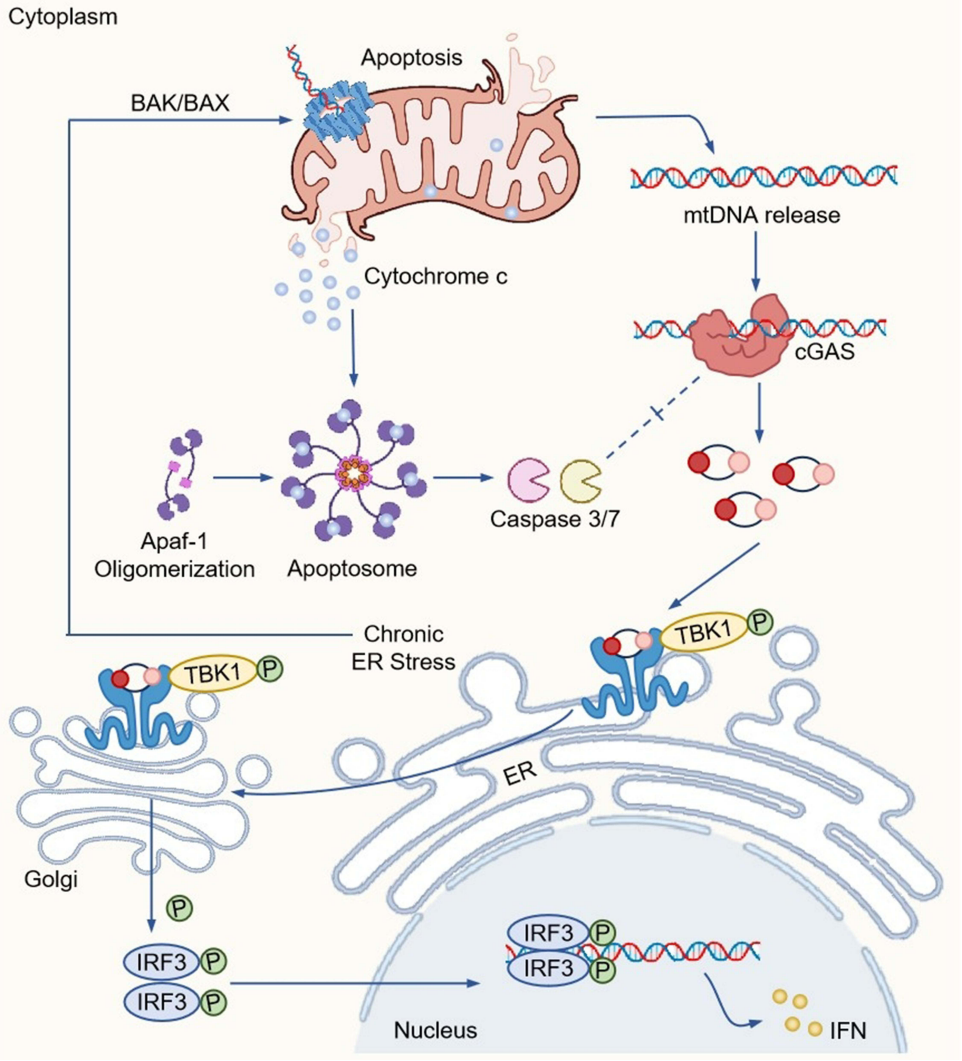

Figure 2 Mechanism of STING-mediated apoptosis regulation. During apoptotic signaling, pro-apoptotic proteins such as BAK/BAX induce mitochondrial membrane permeabilization, leading to the release of cytochrome c and mitochondrial DNA (mtDNA). The released mtDNA activates the cGAS-STING-TBK1 pathway, driving IFN-mediated immune responses. Concurrently, cytosolic cytochrome c facilitates the assembly of the Apaf1-caspase-9 apoptosome, which subsequently activates effector caspases (eg, caspase-3 and caspase-7) to execute apoptosis. Caspase-3 negatively regulates the cGAS-STING pathway by cleaving IRF3 and STING. On the other hand, STING activation triggers ER stress, ultimately leading to apoptosis through BAK/BAX activation and cytochrome c release. This intricate interplay highlights the dual roles of STING in modulating apoptosis and immune responses.

Pyroptosis

Pyroptosis is a form of programmed cell death mediated by cysteine proteases (caspase-1/4/5/11),[84] with three main pathways. The classical pathway relies on Caspase-1, which cleaves the inflammasomes NLR family pyrin domain containing 3 (NLRP3), absent in Melanoma 2 (AIM2), NLR family pyrin domain containing 1 (NLRP1), PYRIN, and NOD-like receptor family CARD domain-containing protein 4(NLRC4), as well as the precursors of inflammatory cytokines (such as pro-IL-1β and pro-IL-18) to cleave Gasdermin D.[85,86] This results in the formation of membrane pores, leading to cell membrane rupture and the release of inflammatory cytokines, thereby triggering pyroptosis.[36,37] The non-classical pathway depends on Caspase-4/5/11,[39] which directly recognize pathogen-associated lipopolysaccharides (LPS), cleave Gasdermin D, and form membrane pores, thus inducing pyroptosis. The third pathway relies on Caspase-3/8, which cleave Gasdermin E and induce an incomplete form of pyroptosis,[87,88] primarily exerting an inflammatory cleavage function.

In sepsis-associated ALI, pyroptosis is often accompanied by overexpression of pro-inflammatory mediators and exacerbation of lung tissue damage.[89] For instance, in ARDS patients, levels of Caspase-1, IL-1β, IL-18, and TNF-α are

significantly higher than in healthy individuals, with more severe lung injury observed in patients with poor prognosis.[90,91] Studies have shown that modulating macrophage pyroptosis could become a potential therapeutic target for ALI.[92–97] Macrophage pyroptosis can be influenced by factors such as regulation of mitochondrial function,[92,93] exosomes,[94] the generation of neutrophil extracellular traps,[89] and control of upstream signaling,[95–97] thus impacting the development and outcome of ALI.

STING regulates pyroptosis through various mechanisms, with the primary pathway involving the cGAS-STING-NLRP3 signaling axis (Figure 3).[34] After cGAS-STING detects cytoplasmic DNA, activated STING is transported to the lysosome, where it increases membrane permeability and triggers lysosomal cell death (LCD). This, in turn, activates potassium efflux upstream of NLRP3 and triggers activation of the classical NLRP3 inflammasome. Additionally, STING promotes inflammasome activation by recruiting NLRP3 to the endoplasmic reticulum and weakening NLRP3 polyubiquitination.[32] STING also acts as a proton channel, inducing proton leakage to activate NLRP3.[33] However,

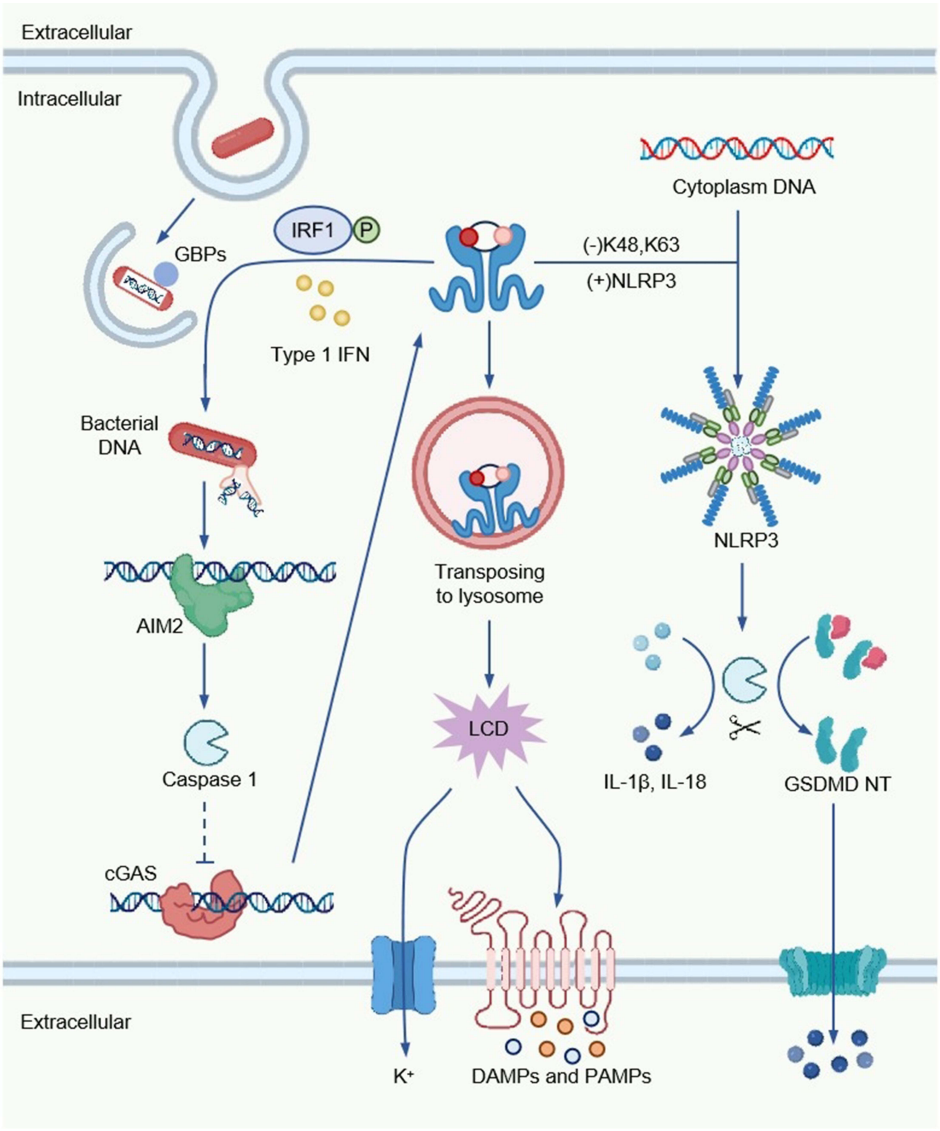

Figure 3 Mechanism of STING-mediated pyroptosis regulation. STING modulates pyroptosis primarily through the cGAS-STING-NLRP3 signaling axis, where cytosolic DNA detection activates STING, leading to lysosomal cell death (LCD). This process triggers K^+ efflux and the release of DAMPs/PAMPs, which promotes NLRP3 inflammasome activation. STING promotes inflammasome activation by recruiting NLRP3 to the ER membrane (via K48/K63-deubiquitinated NLRP3) and inducing proton leakage. However, there is cross-regulation within intracellular DNA sensing pathways, such as caspase-1 cleaving cGAS to inhibit IFN production. In sepsis-associated acute lung injury, STING/IRF3 signaling inhibits NLRP3-mediated macrophage pyroptosis can alleviate lung damage, highlighting the potential therapeutic target of the cytoplasmic DNA-STING-NLRP3 axis.

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there is cross-regulation within the intracellular DNA sensing pathways. For example, Caspase-1 can cleave cGAS to inhibit its mediated IFN production.[35] Other inflammasomes also negatively regulate the cGAS-STING pathway. NLRC3 directly interacts with STING to prevent its translocation to the perinuclear region and binding with TANK-binding kinase 1(TBK1), thereby blocking IFN response and NF-κB activation.[40] NLRP4 negatively regulates type I interferon signaling by targeting the kinase TBK1 for degradation via the E3 ligase DTX4.[41] During *Francisella* infection, STING can drive IRF1-mediated enhancement of type I interferons, stimulate GBP expression, and activate AIM2 inflammasomes, which then recruit Caspase-11 to induce pyroptosis.[38] In sepsis-associated acute lung injury, STING/IRF3-dependent inhibition of NLRP3-mediated macrophage pyroptosis can alleviate lung injury.[98] Furthermore, LPS can activate STING through a cytoplasmic DNA-dependent manner and upregulate STING expression in a c-Myc-dependent manner, promoting ALI. The cytoplasmic DNA-STING-NLRP3 axis is a potential therapeutic target.[96]

Necroptosis

Necroptosis is a regulated form of cell death activated by proteins such as receptor-interacting protein kinase 1(RIPK1), receptor-interacting protein kinase 3(RIPK3), and mixed lineage kinase domain-like pseudokinase (MLKL).[99,100] The activation of RIPK1 is the initial step and can be triggered by factors such as TNF, FasL, and TRAIL.[101–103] Upon binding of TNF to TNFR1, a membrane-associated complex I is formed, leading to the deubiquitination of RIPK1,[104,105] which causes the dissociation of RIPK1 from TRADD and triggers necrosis. In the absence of caspase-8, RIPK1 activates RIPK3,[106,107] which then phosphorylates MLKL, inducing conformational changes that disrupt the plasma membrane integrity,[108,109] leading to the leakage of cellular contents, including DAMPs, which activate immune cells and induce a robust inflammatory response.[110]

In sepsis-associated ALI, necroptosis plays a key role.[111] Several sepsis models have confirmed the presence of necroptosis in lung tissue,[112–116] and the upregulation of RIPK3 mediated by STIM-1 in pulmonary endothelial cells is associated with vascular inflammation.[112] In alveolar epithelial and endothelial cells, necroptosis can improve lung injury and prognosis in septic mice by knocking out RIPK3,[113] manifested by reduced alveolar congestion, hemorrhage, neutrophil infiltration, and the formation of alveolar walls/ hyaline membranes, alongside decreased MLKL expression. Studies by Sharma, Matsuo and Hansen, Jacob further support these findings.[114,115] Additionally, research in human sepsis-associated ARDS shows that plasma RIPK3 levels are correlated with mortality and the respiratory component of the sequential organ failure assessment (SOFA) score.[116]

Necroptosis is closely associated with the cGAS-STING pathway, as both IFN and TNF-α signaling can trigger necroptosis (Figure 4). Type I interferons can drive macrophage necroptosis during *Salmonella typhimurium* infection. Mice with IFNAR1 deficiency show increased survival, and RIP3-deficient macrophages exhibit reduced cell death and enhanced infection control.[46] Further studies have shown that IFN-I upregulates RIP3 and Pgam5, inhibits Nrf2-dependent antioxidant gene transcription, and disrupts redox homeostasis, impairing the body's response to infection-induced oxidative stress.[42] Moreover, constitutive interferon signaling maintains MLKL expression to promote necroptosis.[45] Similarly, Zhang, Wu proposed that mtDNA-STING signaling induces necroptosis in a STING-dependent manner through IFN and TNF-α production. IFNAR-IN and SPD304 can reduce mtDNA-mediated necroptosis.[43] Schock, Chandra also suggested that necroptosis induced during viral infections requires the activation of the adaptor molecule STING and is TNF-dependent.[47] Furthermore, studies have revealed a TNF-driven amplification mechanism of necroptosis signaling. PUMA promotes mitochondrial DNA release and the activation of DAI/Zbp1 and STING, enhancing RIP3 and MLKL phosphorylation, which forms a positive feedback loop.[48] In sepsis-associated acute lung injury, IFN and TNF-α are widely activated, and necroptosis is closely related to STING signaling. Zhang, Wu further demonstrated that RIPK3 inhibits STING autophagy to maintain its signaling activation, whereas MLKL modulates STING in the opposite manner.[44] Blocking MLKL oligomerization and translocation can reduce inflammatory cytokines and IFN-stimulated gene expression, inhibiting STING phosphorylation and activation, a process that occurs before TBK1 recruitment. Additionally, this study showed that inhibition of necroptosis signaling could prevent sepsis-induced multiorgan dysfunction and systemic inflammation in septic shock patients.

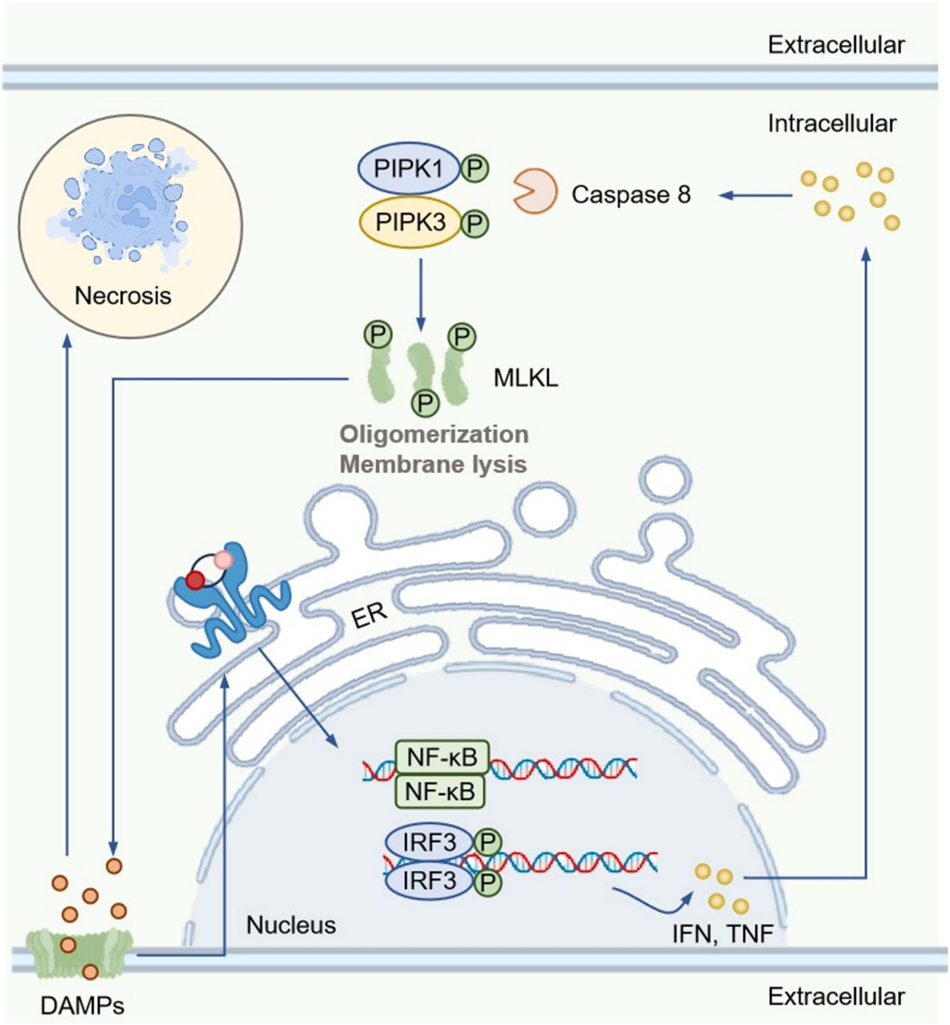

Figure 4 Mechanism of STING-mediated necroptosis regulation. RIPK1 and RIPK3 are essential kinases that modulate necroptosis, forming a functional amyloid signalosome complex that mediates the phosphorylation of MLKL. Phosphorylated MLKL induces membrane lysis and necroptosis. Activation of the STING pathway triggers the production of type I IFNs and TNF, initiating necroptosis through the RIPK1/RIPK3/MLKL signaling cascade. Necroptosis leads to cell membrane disruption and the release of intracellular contents, including DAMPs, which further activate the STING pathway, establishing a positive feedback loop. This intricate mechanism highlights the role of STING in regulating necroptosis and inflammation.

Autophagy

Autophagy is a cellular degradation and recycling mechanism that primarily includes macroautophagy, microautophagy, chaperone-mediated autophagy (CMA), and selective autophagy.[117–119] Macroautophagy is the predominant form of autophagy, involving several steps: the initiation phase is activated by the ULK1 complex,[120] the nucleation phase depends on the Beclin1 complex and the production of PI3P,[121–123] the elongation phase involves the ATG12-ATG5-ATG16L complex and the lipidation of LC3 to form autophagosomes,[124–128] and finally, the autophagosomes fuse with lysosomes to degrade their contents.[129,130] Microautophagy is a process where lysosomes directly engulf cytoplasmic components; it is relatively simple, but its mechanism is not yet fully understood.[131] CMA involves molecular chaperone proteins that recognize proteins containing specific sequences and transport them to lysosomes for degradation.[132] Selective autophagy specifically removes certain cellular components, such as mitophagy, which clears damaged mitochondria through PINK1 and Parkin,[133] endoplasmic reticulum (ER) autophagy, which eliminates stressed ER,[134] and xenophagy, which removes invading pathogens. The autophagy process is finely regulated by signaling pathways such as mTOR and AMPK to adapt to the cell's energy status and stress needs.[135–137]

STING regulates autophagy through various mechanisms (Figure 5). On one hand, STING can activate autophagy in both cGAS-dependent and -independent manners. cGAMP activates downstream STING signaling, promoting an

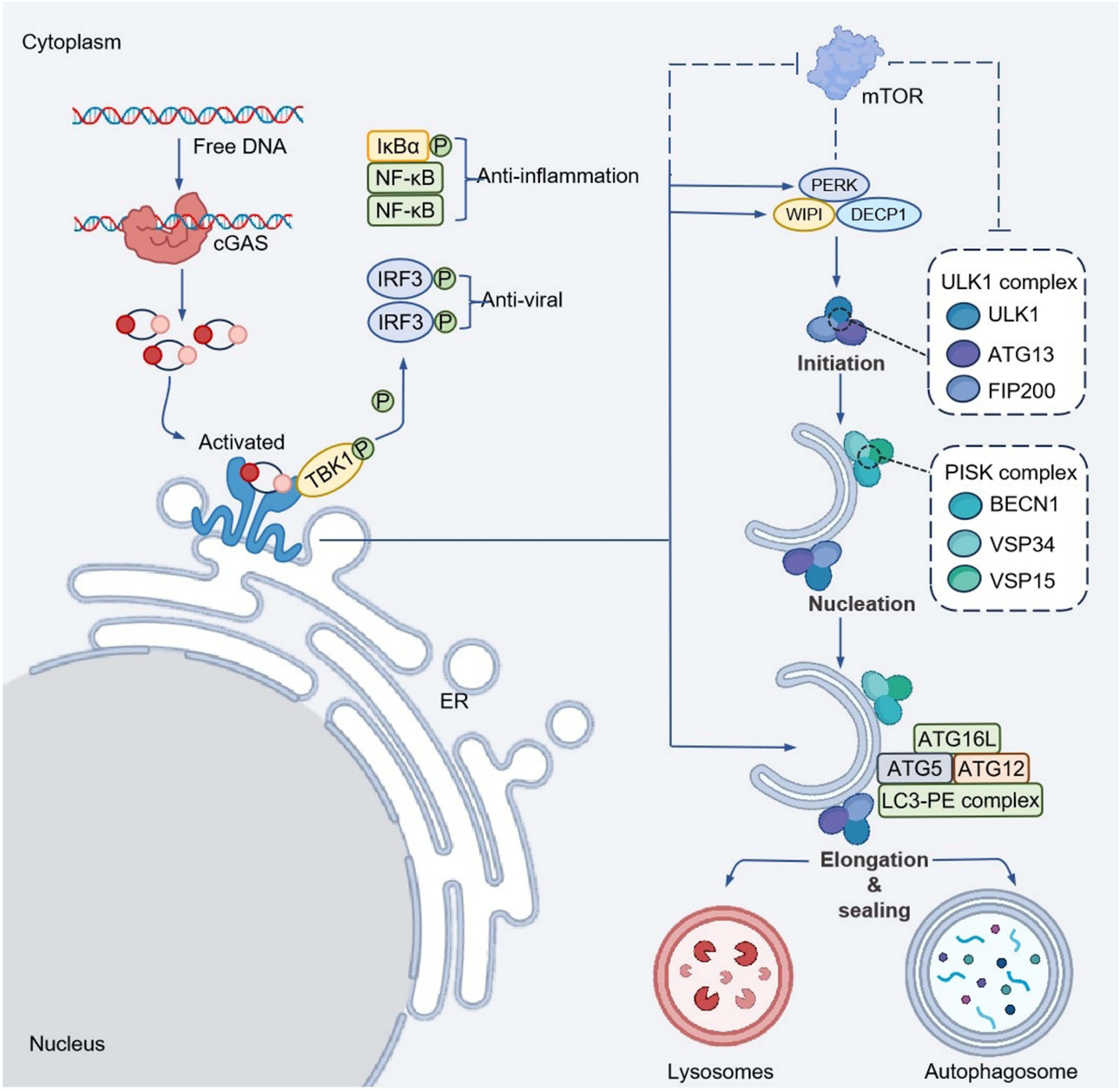

Figure 5 Mechanism of STING-mediated autophagy regulation. Autophagy, a cellular degradation and recycling mechanism, involves steps initiated by the ULK1 complex, nucleation dependent on the PI3K complex, and elongation/sealing mediated by the LC3-PE complex. The autophagosome ultimately fuses with lysosomes for cargo degradation. The STING pathway modulates autophagy through dual mechanisms: activation and inhibition. Activation occurs via cGAS-dependent and -independent pathways, enhancing LC3-II levels and reducing p62, while inhibiting mTOR to induce ERphagy. Conversely, excessive STING activation can impair lysosomal acidification and block autophagic flux. Additionally, STING can suppress autophagy by increasing ULK1 phosphorylation and enhancing mTOR activity. Negative feedback regulation exists where autophagy degrades STING to prevent overactivation of the cGAS-STING pathway. This intricate regulation is crucial for cellular homeostasis and immune responses, particularly in the context of sepsis-associated acute lung injury.

increase in LC3-II and a decrease in p62 levels,[50,138] and the interaction between cGAS and Beclin-1 can release autophagy-negative regulators, such as Rubicon, thereby activating the PI3K complex.[52] Furthermore, upon activation, STING can interact with ATG16L1 and V-ATPase to induce LC3 lipidation,[49] or it can interact with the PERK signaling pathway to inactivate mTOR and induce ER autophagy.[53] On the other hand, STING can also inhibit autophagy. In sepsis-associated ALI models, excessive activation of STING leads to abnormal lysosomal acidification and blockage of autophagic flux,[139] inhibiting autophagy degradation. Overexpression of STING reduces the expression of autophagy-related proteins, and phosphorylation of the S757 site on ULK1 increases, thereby inhibiting autophagy initiation.[51]

When hepatocytes are stimulated by palmitic acid, STING activation enhances mTOR activity and inhibits autophagy initiation.[54] Additionally, under nutrient-rich conditions, STING binds with STX17 to inhibit the fusion of autophagosomes with lysosomes, reducing autophagic activity. In contrast, during cellular starvation or STING pathway activation, STX17 is released, upregulating autophagy and promoting cellular energy metabolism.[56]

There is also a feedback regulation between the STING pathway and autophagy. Autophagy can suppress the overactivation of the cGAS-STING pathway by degrading STING (eg, through the p62/SQSTM1-dependent pathway or via CCDC50 and UXT proteins).[50,140,141] Moreover, the autophagy-related protein Beclin-1 can bind to cGAS, inhibiting its activity and reducing cGAMP production, thereby suppressing STING activation;[52] AMPK and ULK1 phosphorylate the S366 site of STING to promote its degradation, achieving negative feedback regulation.[55] Autophagy can also clear cytoplasmic DNA, alleviating excessive activation of the STING pathway and tissue damage.[50,52,55,140–142] Although both the cGAS-STING pathway and autophagy are significantly activated in sepsis-associated acute lung injury, some of their regulatory mechanisms still require further confirmation.

Ferroptosis

Ferroptosis is a type of cell death dependent on iron ions, with its mechanisms primarily involving iron accumulation, lipid peroxidation, and disruption of antioxidant defense systems.[143–145] An increase in intracellular iron ions catalyzes the Fenton reaction with hydrogen peroxide, producing reactive oxygen species (ROS),[146] which initiate the lipid peroxidation of polyunsaturated fatty acids (PUFAs).[147] Under the action of ACSL4 and LPCAT3, PUFAs are esterified into phosphatidylethanolamines (PEs) and subsequently oxidized to lipid peroxides by lipoxygenases.[148–151] Meanwhile, dysfunction of the cysteine/glutamate antiporter (System Xc^-) impairs glutathione (GSH) synthesis, leading to a decrease in the activity of glutathione peroxidase 4 (GPX4).[152–155] Degradation of ferritin also releases iron ions,[156,157] further exacerbating lipid peroxidation. Together, these factors lead to cellular membrane damage, mitochondrial dysfunction, and ultimately cell death.

In sepsis-associated ALI, ferroptosis regulates cell injury through various pathways. In pulmonary microvascular endothelial cells, miR-125b-5p inhibits ferroptosis through the Keap1/Nrf2/GPX4 axis,[158] whereas CircEXOC5 and STEAP1 promote ferroptosis.[159,160] In lung epithelial cells, m6A modification of GPX4, YAP1, AUF1, and other factors regulate ferroptosis via different mechanisms.[161–164] In lung macrophages, eicosanoid acid, uridine, and H_2S inhibit ferroptosis by activating antioxidant pathways or suppressing lipid peroxidation.[165–168]

In sepsis-associated ALI, the cGAS-STING signaling pathway regulates ferroptosis by modulating lipid peroxidation, iron metabolism, and antioxidant systems. In terms of iron metabolism, STING binds with NCOA4 to promote ferritin degradation, releasing iron ions that trigger lipid peroxidation and enhance STING dimer stability, exacerbating the inflammatory response. This binding also reduces NCOA4 nuclear localization, indirectly promoting ferroptosis.[57] Exosomes secreted by alveolar macrophages containing Ficolin B increase lipid peroxidation products (such as malondialdehyde [MDA]) and iron ion accumulation via the cGAS-STING pathway, lowering GSH levels, intensifying oxidative stress, and leading to autophagy-dependent ferroptosis.[63] STING activation also degrades ferroportin 1 (FPN1), disrupting iron homeostasis and promoting ferroptosis.[59,60] Regarding lipid peroxidation and antioxidant system regulation, GPX4 promotes STING activation by maintaining the redox homeostasis of lipids,[58] and STING increases lipid peroxide generation by regulating ACSL4 activity.[62] STING also inhibits System Xc^- activity, reducing GSH synthesis, indirectly lowering GPX4 activity, weakening the cell's antioxidant capacity, and ultimately leading to ferroptosis.[58,61]

NETosis

NETosis is the process by which neutrophils kill extracellular bacteria through suicidal programmed cell death. The key event is the release of chromatin containing antimicrobial proteins, forming neutrophil extracellular traps (NETs).[169,170] Exogenous stimuli activate various receptors on the surface of neutrophils, such as cytokine receptors, FcγR, TLR, DAMP receptors, C5aR, and adenosine receptors,[171–173] leading to an increase in intracellular calcium ion concentration and activation of protein kinase C (PKC).[171–173] PKC further activates NADPH oxidase-2 (NOX2) or induces mitochondrial dysfunction to generate ROS.[174] At the same time, cyclins CDK4 and CDK6 are activated.[175] PKC-α mediates nuclear membrane rupture, releasing myeloperoxidase (MPO) and elastase (NE), which activate Gasdermin-D (GSDMD)

to form pores on the cell membrane.[65–67] ROS activate PAD4,[64] and PAD4, through histone citrullination, NE-mediated histone cleavage, and MPO oxidation, promotes chromatin decondensation, mixing nuclear content with the cytoplasm. Finally, the inflammasome activates Caspase-11, cleaving GSDMD,[176,177] disrupting membrane integrity, and causing cell membrane rupture, releasing NETs to exert antimicrobial effects.

In sepsis, NETs serve as an effective defense mechanism, blocking and inactivating pathogens, preventing their growth and spread.[178] However, abnormal NET release, particularly in the lungs, is associated with inflammation, immune thrombosis, and worsened tissue damage. Studies have shown that inhibiting Gasdermin D or PAD4 to block NET release can reduce multi-organ dysfunction and ALI in septic mice.[179–181] Elevated circulating NETs in critically ill patients with sepsis-associated ARDS have also been observed, correlating with worse clinical outcomes and directly associated with organ dysfunction.[182–186]

In sepsis-associated ALI, the cGAS-STING pathway plays a crucial role in NETosis, particularly in relation to NETs (Figure 6). NETs participate in lung epithelial cell damage via the cGAS-STING pathway. Pretreating mice with the inhibitor H-151 does not affect cell infiltration in the bronchoalveolar lavage fluid (BALF) or MPO/NE levels, but DNase I can reverse the excessive activation of cGAS-STING in ALI, indicating that cGAS-STING is downstream of NETs.[69] The intracellular communication between inflammatory pathways and the coagulation cascade during sepsis-associated ALI is also linked to NETs. The NETs-STING-TF axis activates STING via the TLR2 receptor, inducing tissue factor (TF) expression in endothelial cells, amplifying the imbalance between inflammation and coagulation.[70] STING activation in platelets similarly affects NETosis and septic thrombosis, modulating granule secretion and platelet activation through interactions with STXBP2. P-selectin mediates neutrophil-platelet aggregation, promoting NETosis.[71] Furthermore, mitochondrial dysfunction and mtDNA release mediated by GSDMD cleavage promote neutrophil extracellular trap formation through the mtDNA-cGAS-STING pathway, ultimately worsening lung injury.[68]

PANoptosis

PANoptosis is a programmed cell death mode that integrates features of pyroptosis, apoptosis, and necroptosis. The core of PANoptosis is the assembly and activation of the PANoptosome.[187–189] When cells are subjected to infection, homeostatic changes, or oxidative stress, receptors (such as ZBP1, AIM2, RIPK1, etc) are activated and recruit molecules to form the PANoptosome. This complex consists of PAMPs/DAMPs sensors (such as ZBP1, AIM2, NLRP3), adaptors (such as ASC, FADD), and catalytic effectors (such as RIPK1, RIPK3, CASP1, CASP8),[72,73,190–192] which can induce caspase activation, GSDMD/GSDME cleavage, and MLKL phosphorylation, leading to the loss of cell membrane integrity, leakage of cellular contents, and triggering of inflammation.[193] PANoptosis is regulated by multiple molecules (such as IRF1, TAK1, ADAR1) and organelle functions.[194–196] As a highly pro-inflammatory form of cell death, excessive PANoptosis can also lead to tissue damage and disease development.

In the LPS-induced acute lung injury model, several studies have demonstrated similar results.[74,197] Upon STING activation, through the TBK1-IRF3 axis and NF-κB pathway interactions, the expression and activation of GSDMD are affected, leading to pyroptosis; Caspase-8 expression and activation are affected, triggering apoptosis; and the expression and phosphorylation of MLKL are influenced, promoting necroptosis. Inhibiting the STING pathway using KAE or UDCA suppresses the assembly and activation of the PANoptosome complex,[74,197] thereby reducing PANoptosis and alleviating sepsis-induced acute lung injury. Messaoud-Nacer, Culerier also demonstrated that using the STING agonist diABZI to induce programmed cell death resulted in characteristics of pyroptosis,[18] apoptosis, and necroptosis, ie, PANoptosis. This regulatory mechanism appears to be universal.[75,76,198,199] In diffuse large B-cell lymphoma (DLBCL), SAMHD1 deficiency induces STING expression, activating the cGAS-STING pathway, promoting the formation of the Caspase 8/RIPK3/ASC complex, leading to MLKL phosphorylation, Caspase 3 cleavage, and GSDME cleavage, triggering STING-mediated PANoptosis.[75] In sepsis-induced Kupffer cell PANoptosis, heme and bacteria act together to cause mitochondrial damage, release mtDNA, and activate the cGAS-STING pathway, exacerbating PANoptosis.[76]

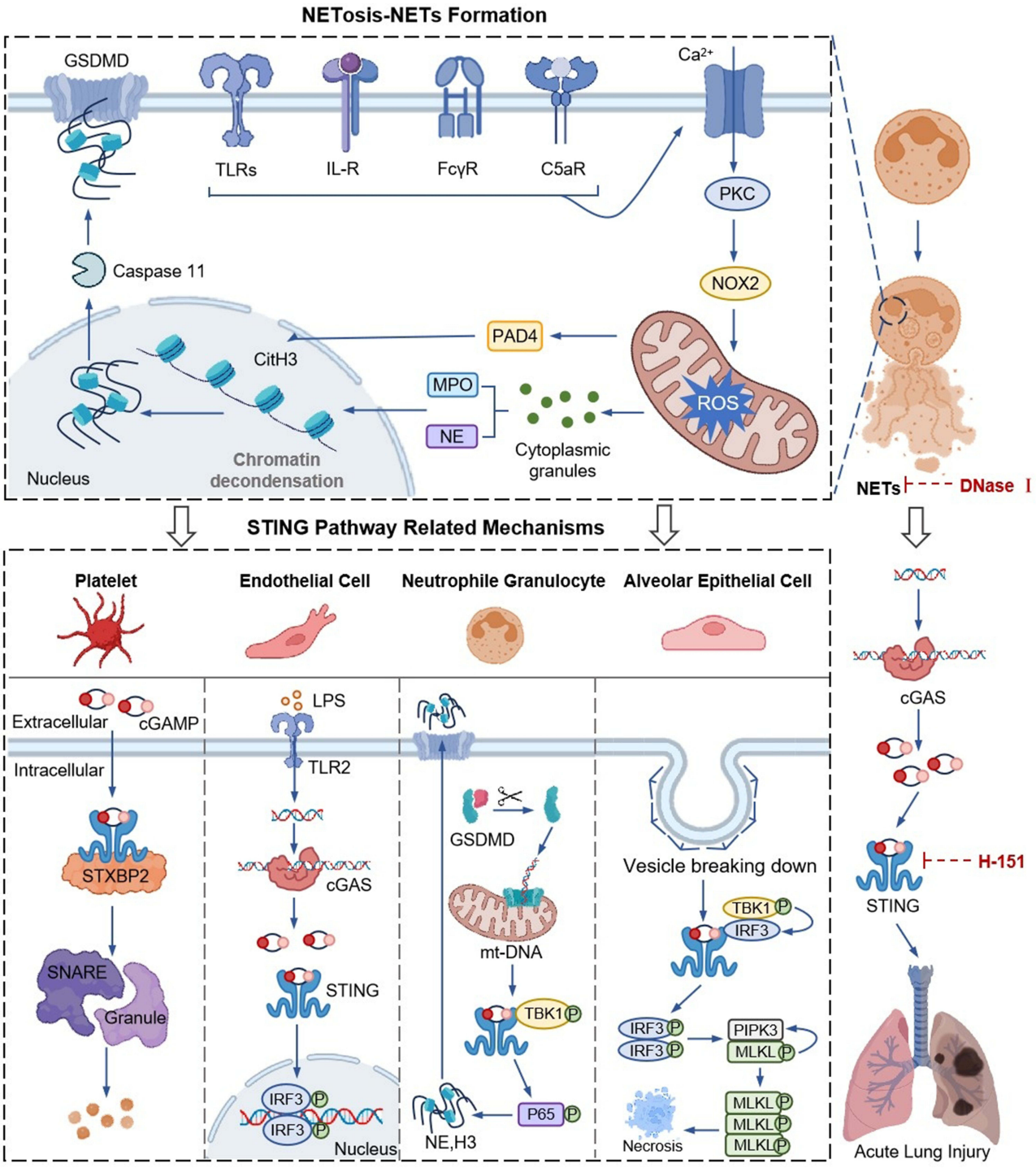

Figure 6 Mechanism of STING-mediated NETosis regulation. The cGAS-STING pathway, operating downstream of NETs, exacerbates lung injury, which can be mitigated by inhibiting NET formation with DNase I or STING with H-151. Mechanism 1: STING activation in platelets enhances platelet activation and granule secretion, worsening sepsis-induced thrombosis. Platelet-specific STING deficiency reduces thrombosis and NETosis in mice. Mechanism 2: NETs activate endothelial cells via STING, inducing tissue factor (TF) expression and amplifying the imbalance between inflammation and coagulation, with TLR2 on endothelial cells mediating this interaction. Mechanism 3: The mtDNA-cGAS-STING pathway promotes NET formation through GSDMD-N cleavage, leading to mitochondrial dysfunction and mtDNA release, activating the cGAS-STING pathway and resulting in NETs and lung injury. Mechanism 4: Alveolar epithelial cells (AECs) internalize NETs, activating the cGAS-STING pathway and triggering necroptosis, promoting ALI in mice. These mechanisms highlight the critical role of the STING pathway in modulating NETosis and its implications in acute lung injury.

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Conclusion

In summary, the crosstalk between diverse cell death mechanisms—including apoptosis, pyroptosis, necroptosis, autophagy, ferroptosis, NETosis, PANoptosis—and the cGAS-STING pathway critically drives inflammation and tissue damage in sepsis-associated acute lung injury. This intricate interaction, regulated by cGAS-STING, collectively amplifies ALI severity. Emerging therapeutic strategies highlight the potential of targeting this pathway, such as STING inhibition to reduce macrophage ferroptosis and inflammation, alongside exosome-based molecules that modulate immunity and promote tissue repair.

Despite these advances, significant knowledge gaps persist regarding the precise molecular mechanisms of cGAS-STING coordination of multiple death modalities, for example how it simultaneously regulates PANoptosis components like GSDMD, caspase-8, and MLKL. The cell-type-specific roles and contributions of the pathway in alveolar epithelial, endothelial, and immune cells also remain poorly defined, along with validated dynamic STING-autophagy and STING-ferroptosis feedback loops in sepsis, and biomarkers for patient stratification. Future research must prioritize mechanistic dissection using cell-specific knockout models and spatial transcriptomics to resolve crosstalk such as the STING-RIPK3 /MLKL axis. It should also develop combination therapies integrating STING inhibitors like H-151 with agents targeting downstream effectors such as NLRP3 blockers or ferroptosis inhibitors like Liproxstatin-1 to overcome compensatory resistance, advance delivery systems for engineered exosome therapies carrying STING-siRNA to enhance lung targeting, and translate preclinical findings clinically through phase-selective interventions and biomarker-driven stratification using plasma mtDNA and NETs levels as STING activation indicators. Combining deep mechanistic insights with these targeted therapeutic strategies is crucial for developing effective interventions to improve sepsis-associated ALI outcomes.

Data Sharing Statement

No datasets were generated or analyzed during the current study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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