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REVIEW

Novel Perspectives in Hepatic Ischemia-Reperfusion Injury: The cGAS-STING Pathway

Runsheng Chen[1,*], Tingfeng Yang[1,*], Zhonghao Jiang[1], Yang Long[2], Baolin Qian[1,3], Wenguang Fu[1,3]

[1]Department of Biliary-Pancreatic Center, The Affiliated Hospital of Southwest Medical University, Luzhou, People's Republic of China; [2]Department of Endocrinology and Metabolism, The Affiliated Hospital of Southwest Medical University, Luzhou, People's Republic of China; [3]Metabolic Hepatobiliary and Pancreatic Diseases Key Laboratory of Luzhou City, Academician (Expert) Workstation of Sichuan Province, The Affiliated Hospital of Southwest Medical University, Luzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wenguang Fu; Baolin Qian, Email fuwg@swmu.edu.cn; qianbl@swmu.edu.cn

Abstract: In hepatic ischemia-reperfusion injury (HIRI), the cGAS-STING pathway serves as a central regulatory hub by sensing aberrant mitochondrial DNA (mtDNA) release. Ischemia-reperfusion triggers mtDNA leakage through mechanisms including mitochondrial permeability transition pore (mPTP) opening, voltage-dependent anion channel (VDAC) oligomerization, and excessive fission. Cytosolic mtDNA activates cyclic GMP-AMP synthase (cGAS), catalyzing the synthesis of cGAMP, which stimulates stimulator of interferon genes (STING) oligomerization and translocation. This activates the TBK1-IRF3/NF-κB axis, driving expression of type I interferons (IFN-I) and pro-inflammatory cytokines, thereby amplifying neutrophil infiltration, macrophage pyroptosis, and hepatocyte apoptosis. The pathway bidirectionally interacts with oxidative stress and mitophagy, exhibiting cell-type specificity: in hepatocytes, cGAS promotes protective STING-independent autophagy, whereas in macrophages, STING drives inflammatory activation. Targeted inhibition of cGAS-STING signaling and mitochondrial stabilization represent promising therapeutic strategies.

Keywords: cGAS-STING pathway, hepatic ischemia/reperfusion injury, inflammatory response, oxidative stress, cell death

Introduction

Hepatic ischemia-reperfusion injury (HIRI) constitutes an inevitable pathological process in surgical procedures such as liver transplantation, resection, and trauma repair. It represents a significant direct cause of postoperative liver failure, graft failure, and even mortality.[1–3] The pathological mechanisms of HIRI involve multi-layered interactions, encompassing the synergistic activation of oxidative stress, mitochondrial dysfunction, dysregulated inflammatory responses, and programmed cell death.[4–6] Although existing research has partially elucidated the roles of signaling axes such as MAPK and TAK1/ASK1, the core regulatory network remains incompletely resolved, impeding the development of targeted therapies.[7]

Cyclic GMP-AMP synthase (cGAS) is a central DNA sensor in the innate immune system. Upon sensing aberrant cytosolic double-stranded DNA (dsDNA), such as pathogen-derived DNA, mitochondrial DNA (mtDNA), or nuclear DNA (nDNA) released during damage, cGAS triggers broad immune responses.[8] Following dsDNA binding, cGAS catalyzes the synthesis of the second messenger cyclic GMP-AMP (cGAMP). cGAMP activates the endoplasmic reticulum-resident protein stimulator of interferon genes (STING), driving its oligomerization and initiating the TBK1-IRF3/NF-κB signaling cascade. This cascade ultimately induces the expression of type I interferons (IFN-I) and pro-inflammatory cytokines.[9] As the cGAS-STING pathway regulates diverse processes—including inflammation, antiviral

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responses, antitumor immunity, cellular senescence, and programmed cell death—it profoundly influences tissue homeostasis and pathological progression.[10–13] Consequently, gaining deeper insights into the cGAS-STING signaling pathway positions it as a critical therapeutic target across multiple disease contexts.

Recent studies indicate that the cGAS-STING signaling pathway is closely associated with the occurrence and progression of ischemia-reperfusion injury.[14] However, a more systematic review of cGAS-STING's role in HIRI is lacking. In this review, we summarize the pathway's activation and functions in HIRI, and outline related inhibitors, to facilitate the development of treatments for HIRI.

Molecular Mechanisms of cGAS-STING Pathway

The cGAS protein consists of a non-conserved N-terminal disordered domain and a highly conserved C-terminal catalytic domain. The C-terminal catalytic domain adopts a bilobed structure.[15] This domain contains the nucleotidyltransferase active site, which catalyzes the synthesis of cGAMP using ATP and GTP, and possesses three key DNA-binding interfaces: sites A and B cooperatively bind dsDNA to form a 2:2 cGAS-DNA dimer, while site C promotes the formation of cGAS-DNA phase-separated condensates via multivalent interactions with long, bent dsDNA, significantly enhancing enzymatic activity.[16,17] The N-terminal disordered region augments DNA-binding capacity through non-specific charge interactions and synergizes with sites A/B/C of the C-terminal catalytic domain to establish multivalent interactions, collectively constituting the key structural basis for cGAS phase separation.[18]

cGAS, as a cytosolic DNA sensor, recognizes aberrantly localized cytosolic dsDNA, including exogenous pathogen DNA and endogenous mislocalized DNA. Intriguingly, cGAS exhibits typical length-dependent, but sequence-independent DNA recognition. Studies indicate that dsDNA ≥20 bp constitutes the fundamental threshold for cGAS activation, while dsDNA shorter than 20 bp fails to support stable dimer formation, resulting in insufficient enzymatic activity. Furthermore, long-chain DNA (≥45 bp) induces cGAS to form more stable "ladder-like oligomers", significantly enhancing cGAS catalytic efficiency through cooperativit.[19,20] Upon binding long dsDNA, cGAS undergoes substantial conformational rearrangement within its catalytic domain, catalyzing the synthesis of the second messenger 2',3'-cGAMP from ATP and GTP.[21,22]

Subsequently, STING, functioning as an endoplasmic reticulum (ER)-localized transmembrane receptor, undergoes significant conformational changes in its C-terminal ligand-binding domain (LBD) upon specific recognition of cGAMP, releasing its autoinhibited state. The activated STING assembles into linear, single-layered polymers via the synergistic action of lateral stacking within the LBD and its transmembrane domain (TMD).[23] This oligomerization promotes the trafficking of STING from the ER to the Golgi apparatus via the COPII complex-mediated vesicular trafficking system.[24,25] Upon reaching the Golgi apparatus, STING undergoes palmitoylation at Cys88 and Cys91 within its N-terminal domain and ubiquitination at Lys224 within the LBD. These post-translational modifications establish the necessary conditions for the recruitment of the kinase TBK1 and the transcription factor IRF3.[26–28]

Following recruitment to SITNG, TBK1, activated by autophosphorylation, directly phosphorylates the C-terminal domain of STING at Ser366. This phosphorylation event creates a specific binding site (the pLxIS motif) for IRF3.[29] IRF3 is recruited to the STING-TBK1 complex via this phosphosite and undergoes TBK1-mediated phosphorylation within the Golgi apparatus.[30] The phosphorylated IRF3 forms dimers that translocate into the nucleus. There, it binds to interferon-stimulated response elements (ISREs), initiating the transcription of IFN-I (primarily IFN-β) and further inducing the expression of downstream interferon-stimulated genes (ISGs).[31,32] Concurrently, STING can also recruit IKK kinases, leading to IκBα phosphorylation and subsequent activation of the NF-κB signaling pathway. This promotes the transcriptional expression of pro-inflammatory cytokines such as TNF-α and IL-6.[33]

Ultimately, activated STING is targeted to the lysosome for degradation via two distinct pathways: (1) A portion of STING is engulfed by autophagosomes, forming double-membrane structures that are delivered to lysosomes through the WIPI2-ATG5-dependent non-canonical autophagy pathway; (2) Another portion traffics through the multivesicular body (MVB) pathway, transported via late endosomes to lysosomes. This entire degradation process is critically dependent on the Rab7a GTPase, whose mediated membrane fusion events constitute a key mechanism for the timely termination of STING signaling.[34] Figure 1 depicts the molecular mechanisms of the cGAS-STING Pathway.

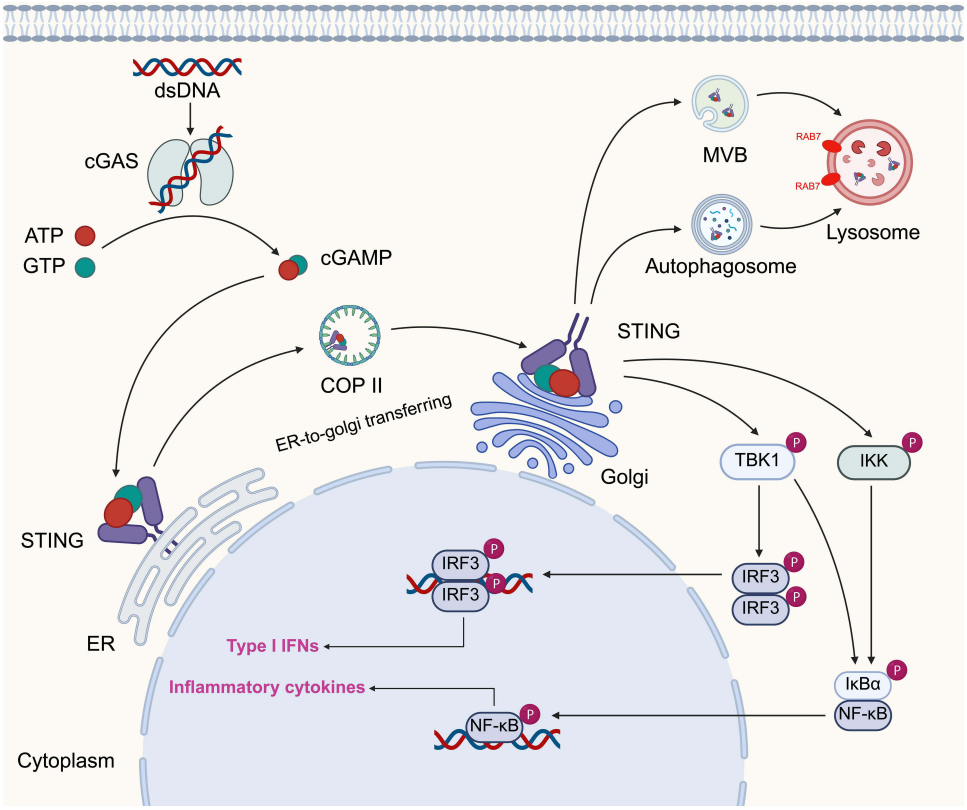

Figure 1 Molecular mechanisms of the cGAS-STING Pathway Cytosolic dsDNA activates cGAS to generate cGAMP from ATP and GTP, which binds and activates STING on the ER. Activated STING translocates to the Golgi via COP II vesicles, where it recruits TBK1 and IKK. TBK1 phosphorylates STING and IRF3, inducing IRF3 dimerization and nuclear translocation to drive IFN-I expression. In parallel, IKK activation releases NF-κB to induce inflammatory cytokines. Finally, STING is degraded through Rab7-dependent autophagy or MVB-lysosomal pathways to terminate signaling. Created with BioRender.com.
Abbreviations: cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; STING, stimulator of interferon genes; ER, endoplasmic reticulum; IFN-I, type I interferons; MVB, multivesicular body.

MtDNA Release Triggers the Activation of cGAS-STING Pathway

In HIRI, the aberrant release of mtDNA serves as a central mechanism initiating the cGAS–STING pathway. Studies have demonstrated that activation of the cGAS–STING pathway is primarily triggered by the release of mtDNA rather than nDNA.[35] Figure 2 illustrates the mechanism of mtDNA release in HIRI.

mPTP Dysregulation in Calcium Overload and ROS-Driven Pore Opening

mPTP, located in the mitochondrial inner membrane, is a non-specific channel whose sustained opening is a key trigger for mtDNA release. mPTP is primarily composed of a protein complex including adenine nucleotide translocase (ANT), VDAC, and cyclophilin D (CyP-D), among which CyP-D is the core regulatory protein of mPTP. The binding of CyP-D to ANT is a critical step for mPTP opening.[36–38]

During hepatic ischemia-reperfusion, cytosolic Ca^2+ concentration increases dramatically. Mitochondria take up large amounts of Ca^2+ via the mitochondrial calcium uniporter (MCU), leading to mitochondrial calcium overload. Excessively high Ca^2+ in the mitochondrial matrix not only lowers the threshold for mPTP opening but also promotes the binding of CyP-D to ANT, inducing the formation of a complex and conformational changes that result in mPTP opening.[39–41] Simultaneously, reactive oxygen species (ROS) enhance the binding affinity of CyP-D to ANT by oxidizing its thiol groups, thereby reducing the threshold for Ca^2+-induced mPTP opening.[37,42]

The opening of mPTP triggers mitochondrial matrix swelling and outer membrane rupture, causing mtDNA leakage into the cytosol.[35,43] Furthermore, in fatty liver ischemia-reperfusion injury, metabolic dysregulation directly exacerbates mtDNA efflux by enhancing the sensitivity of mPTP.[44]

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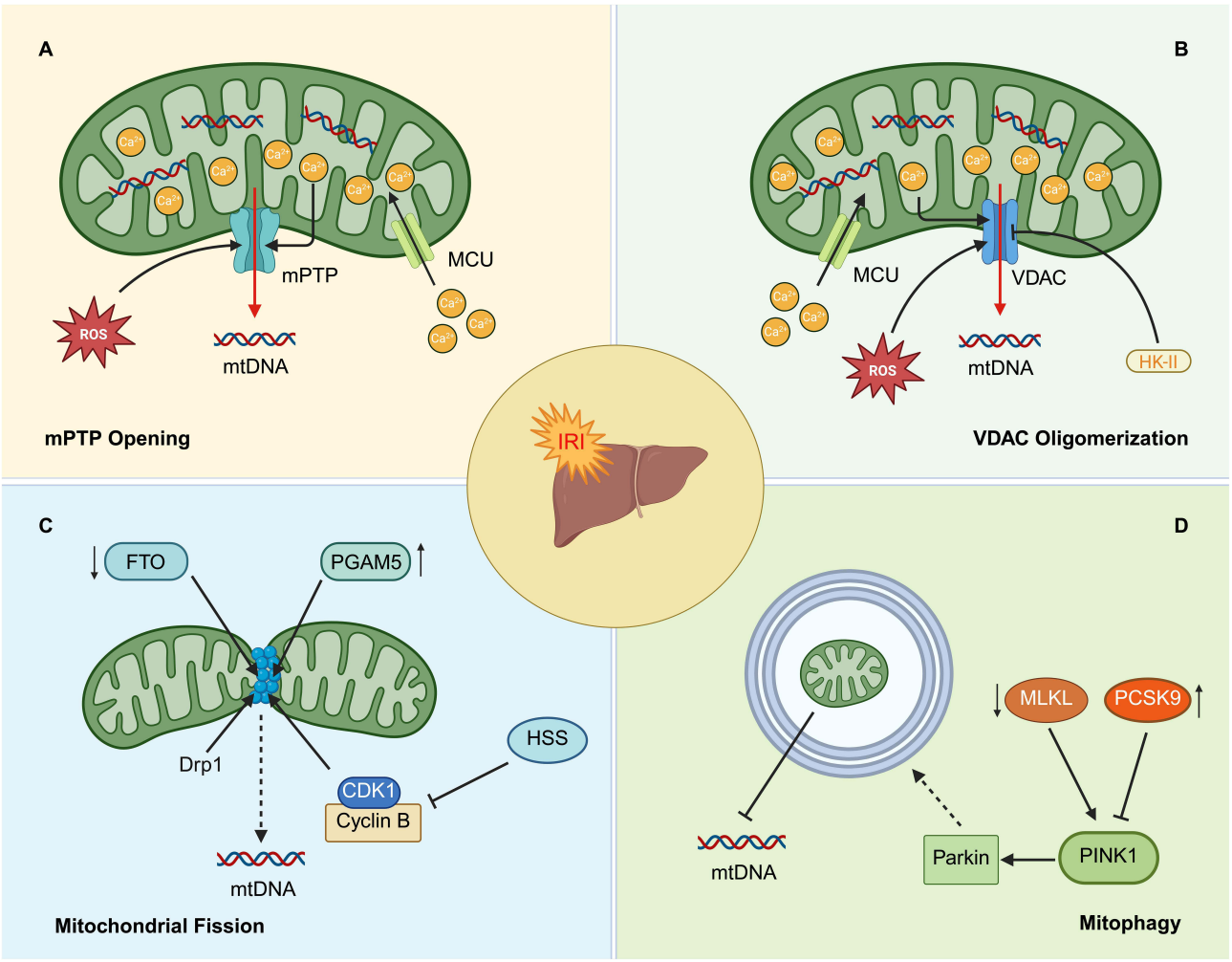

Figure 2 Mechanism of mtDNA release in HIRI Figure 2: HIRI-induced Ca^{2}+ overload and ROS trigger multiple mtDNA efflux pathways: (**A**) mPTP opening via MCU-mediated Ca^{2}+ influx and oxidative stress; (**B**) VDAC oligomerization after HK-II dissociation; (**C**) Drp1-driven mitochondrial fission enhanced by FTO downregulation and PGAM5 upregulation but restrained by HSS inhibition of CDK1/Cyclin B; (**D**) PINK1–Parkin-dependent mitophagy, modulated by MLKL and PCSK9, balancing mtDNA clearance and inflammation. Created with BioRender.com.

Abbreviations: HIRI, hepatic ischemia–reperfusion injury; ROS, reactive oxygen species; mtDNA, mitochondrial DNA; mPTP, mitochondrial permeability transition pore; MCU, mitochondrial calcium uniporter; VDAC, voltage-dependent anion channel; HK-II, hexokinase-II; Drp1, dynamin-related protein 1; FTO, fat mass and obesity-associated protein; PGAM5, phosphoglycerate mutase family member 5; HSS, hepatic stimulator substance; PINK1, PTEN-induced kinase 1; MLKL, mixed-lineage kinase domain-like protein; PCSK9, proprotein convertase subtilisin/kexin type 9.

VDAC Oligomerization Mediating mtDNA Efflux

VDAC, as the primary channel in the mitochondrial outer membrane, directly regulates mtDNA release through its oligomerization state. Under physiological conditions, VDAC exists in a monomeric form, permitting the passage of small molecule metabolites.[45,46] During ischemia-reperfusion, oxidative stress and calcium overload not only induce the opening of mPTP but also promote VDAC oligomerization, forming a large-conductance channel that allows the passage of mtDNA fragments <700 bp, with preferential release of the highly oxidation-damaged D-loop region.[46,47] Furthermore, hexokinase-II (HK-II) inhibits VDAC oligomerization by binding to it under normal conditions, while ischemia-reperfusion causes HK-II dissociation from mitochondria, relieving this inhibition and thereby exacerbating VDAC oligomerization.[48,49]

Imbalance in Mitochondrial Fission/Fusion Dysregulation

The dynamic balance of mitochondrial fission and fusion is crucial for maintaining mtDNA stability. Studies indicate that aberrant activation of Dynamin-related protein 1 (Drp1), a core regulator of mitochondrial fission, is a key mechanism

underlying excessive mitochondrial fission. For instance, the m6A demethylase fat mass and obesity-associated protein (FTO) is significantly downregulated in hepatic I/R injury, resulting in elevated m6A methylation levels of Drp1 mRNA. This methylation modification promotes Drp1 protein expression by enhancing the stability and translation efficiency of Drp1 mRNA, further driving excessive mitochondrial fission and mtDNA leakage.[50] Additionally, phosphoglycerate mutase 5 (PGAM5), functioning as a mitochondrial serine/threonine protein phosphatase, is significantly upregulated during HIRI. By facilitating phosphorylation of Drp1 at the S616 site, PGAM5 enhances Drp1 recruitment to mitochondria, leading to exacerbated mitochondrial fission, loss of mitochondrial membrane potential, and abnormal opening of mPTP, which consequently aggravates mtDNA leakage.[51]

On the other hand, Hepatic stimulator substance (HSS), an anti-apoptotic effector molecule, suppresses mitochondrial fission and maintains mitochondrial integrity by inhibiting the expression of the CDK1/cyclin B complex, thereby reducing Drp1 phosphorylation and its translocation to mitochondria.[52] Therefore, targeting regulatory molecules of the mitochondrial fission/fusion dynamic balance, by reducing abnormal mtDNA release, can subsequently inhibit the overactivation of the cGAS-STING pathway and mitigate HIRI.

The Dual Role of Mitophagy

Mitophagy maintains mtDNA homeostasis by clearing damaged mitochondria, but its excessive activation may trigger "autophagic collapse". The PINK1-Parkin pathway is the core mechanism regulating mitophagy.[53] During HIRI, mitochondrial membrane potential ($\Delta\Psi m$) significantly decreases due to oxidative stress and calcium overload, triggering the stable accumulation of PTEN-induced kinase 1 (PINK1) on the outer mitochondrial membrane (OMM).[54] PINK1 recruits and activates the cytosolic E3 ubiquitin ligase Parkin through phosphorylation, mediating the ubiquitination of mitochondrial membrane proteins (such as VDAC1, TOM20) to form ubiquitinated "eat-me" signals.[55,56] Adaptor proteins such as OPTN/NDP52 recognize the ubiquitin tags and bind to the autophagosome marker microtubule-associated protein 1 light chain 3-II (LC3-II), targeting damaged mitochondria to autophagosomes for degradation, thereby reducing mtDNA leakage.[57]

Research demonstrated that mixed-lineage kinase domain-like protein (MLKL) deficiency significantly enhances hepatocyte capacity to clear damaged mitochondria by activating PINK1-dependent mitophagy. This process effectively reduces abnormal accumulation of ROS and cytosolic leakage of mtDNA under ischemic stress, consequently suppressing cGAS-STING pathway activation and downstream NF-κB-mediated inflammatory responses in macrophages.[58] Furthermore, studies revealed that proprotein convertase subtilisin/kexin type 9 (PCSK9) was upregulated in hepatic I/R injury and significantly impeded the clearance efficiency of damaged mitochondria by inhibiting PINK1-Parkin-mediated mitophagy.[59] This leads to exacerbated mtDNA leakage and hyperactivation of the cGAS-STING pathway.

However, mitophagy exhibits a significant dual role in cellular homeostasis regulation: moderate mitophagy maintains mitochondrial quality by removing damaged organelles, whereas dysregulated autophagic activity—including either excessive activation or complete deficiency—can exacerbate pathological injury. Research indicates that deletion of autophagy-related genes (such as Atg5 or Beclin1) results in dual dysfunctions of mitochondrial quality control: (1) impaired clearance of damaged mitochondria causes sustained opening of mPTP, promoting aberrant leakage of mtDNA into the cytosol and activating the cGAS-STING pathway-mediated inflammatory response; and (2) excessive accumulation of mitochondrial fragments triggers burst accumulation of ROS, subsequently activating mitochondria-dependent apoptotic pathways and aggravating hepatic I/R injury.[60–62] Similarly, excessive mitophagy can also induce aberrant mPTP opening, aggravating mtDNA leakage into the cytosol and leading to more robust cGAS-STING pathway activation.[63] This protective-versus-toxic duality underscores the requirement for precise modulation of mitophagy in maintaining cellular homeostasis.

Bidirectional Regulation of Inflammatory Response and cGAS-STING Pathway

In HIRI, the inflammatory cascade and cGAS-STING pathway activation form a highly interconnected network, as depicted in Figure 3. This process is initiated by the aberrant release of mtDNA into the cytosol, where it acts as a key ligand for activating cGAS. The persistent accumulation of DNA leads to cGAS-catalyzed generation of the second messenger cGAMP, triggering STING protein oligomerization and translocation. This activates the downstream TBK1-

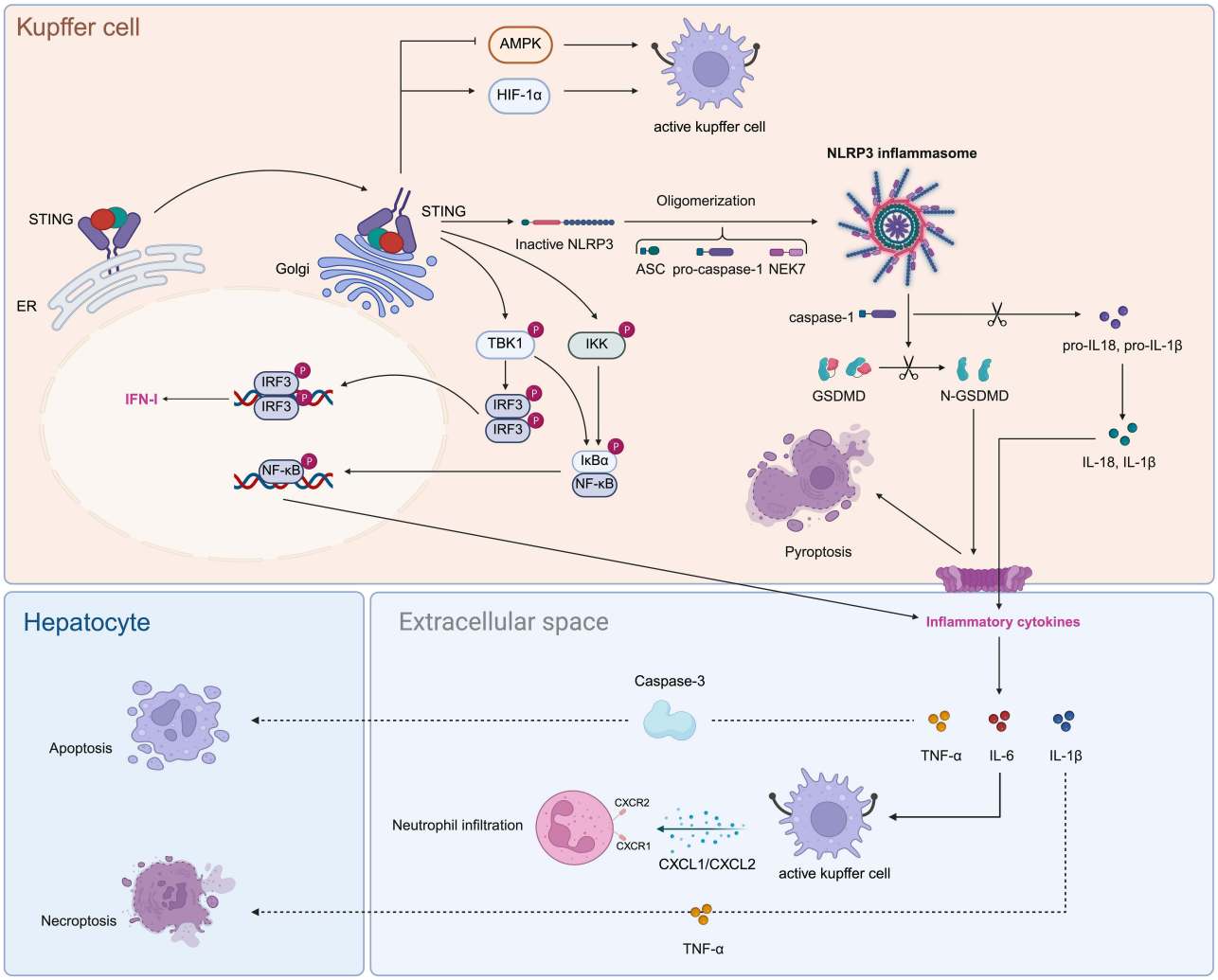

Figure 3 Inflammatory Response and cGAS-STING Pathway Bidirectional Regulation STING activation in KCs triggers TBK1/IKK-dependent IRF3 and NF-κB signaling, inducing IFN-I and pro-inflammatory cytokines. STING also activates the NLRP3 inflammasome, leading to caspase-1/GSDMD-mediated pyroptosis and IL-1β/IL-18 release. STING-TBK1 inhibits AMPK and stabilizes HIF-1α, promoting glycolysis and KC activation. Released TNF-α, IL-6, and IL-1β induce hepatocyte apoptosis/necroptosis and recruit neutrophils via CXCL1/2–CXCR1/2, amplifying liver injury. Created with BioRender.com.
Abbreviations: STING, stimulator of interferon genes; KCs, Kupffer cells; IFN-I, type I interferons; NLRP3, NOD-like receptor family pyrin domain containing 3; GSDMD, gasdermin D; AMPK, AMP-activated protein kinase; HIF-1α, hypoxia-inducible factor 1-alpha; ROS, reactive oxygen species.

IRF3 and NF-κB signaling axes, driving the transcription of IFN-I and pro-inflammatory cytokines (such as TNF-α and IL-6), thereby establishing the initial signal for the inflammatory cascade. Studies have found that age-related defects in immune regulation significantly exacerbate the activation of the cGAS-STING pathway. Following hepatic IR in aged livers, efferocytosis by macrophages is markedly impaired, resulting in reduced clearance efficiency of apoptotic hepatocytes. Subsequently, unengulfed apoptotic cells undergo secondary necrosis, releasing large amounts of immunogenic DNA that enhances STING activation and inflammatory liver injury.[64]

In HIRI, macrophage STING expression is significantly upregulated in the reperfusion phase, emerging as a key driver of inflammation. STING activation remodels macrophage function through dual signaling pathways. First, the STING-TBK1 axis regulates NF-κB activity via the canonical pathway, thereby amplifying pro-inflammatory signaling. In this canonical pathway, activated STING recruits and activates the TBK1/IKKε kinases, which redundantly regulate downstream signaling. TAK1 and the IKK complex (containing IKKα/IKKβ) are activated, leading to the phosphorylation and ubiquitin-mediated degradation of IκB. This releases NF-κB dimers (p65/p50) into the nucleus, initiating the transcription of pro-inflammatory cytokines such as TNF-α and IL-6.[65,66] Studies have demonstrated that inhibiting NF-κB activity in the liver ameliorates short-term hepatic I/R injury.[67]

It is noteworthy that the cGAS-STING pathway not only directly mediates inflammatory responses but also forms a synergistically amplified inflammatory network through crosstalk with other pattern recognition receptors (PRRs). Studies demonstrate that in HIRI, STING signaling directly drives NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation within macrophages, a mechanism particularly pronounced in aged individuals.[68] The activated NLRP3 inflammasome further recruits pro-caspase-1 via the ASC adaptor protein, forming the NLRP3-ASC-caspase-1 complex.[69] Subsequently, auto-proteolytically activated caspase-1 cleaves Gasdermin D (GSDMD) to generate its N-terminal domain (GSDMD-N), which forms pores in the cell membrane, triggering macrophage pyroptosis.[70,71] Concurrently, caspase-1 proteolytically processes the precursors pro-IL-1β and pro-IL-18 in the cytoplasm to generate their mature forms. These mature inflammatory cytokines (IL-1β and IL-18) are then released extracellularly in large quantities through the GSDMD-N pores.[72,73]

Moreover, the STING-TBK1 axis antagonizes the AMPK-mediated anti-inflammatory response and metabolic remodeling (namely, the switch towards oxidative phosphorylation) by suppressing AMP-activated protein kinase (AMPK) phosphorylation and stabilizing hypoxia-inducible factor-1α (HIF-1α) protein. Concurrently, it drives HIF-1α-dependent glycolysis, providing energy for sustained macrophage activation. This metabolic reprogramming not only maintains the hyperactivated state of macrophages but also creates favorable conditions for the further amplification of NF-κB inflammatory signaling, thereby exacerbating metabolic dysregulation and the inflammatory microenvironment.[74]

Ultimately, the excessive release of pro-inflammatory cytokines creates a "cytokine storm", leading to a systemic inflammatory response. Tumor necrosis factor-alpha (TNF-α) induces hepatocyte apoptosis by activating caspase-3 and mediates endothelial barrier disruption via ROS. Interleukin-6 (IL-6) enhances Kupffer cell activation and synergizes with chemokines to amplify neutrophil infiltration. IL-1β cooperates with TNF-α to promote hepatocyte necroptosis. Neutrophil infiltration depends on the binding of the CXCR2 (dominant) and CXCR1 (secondary) receptors to macrophage inflammatory protein-2 (MIP-2/CXCL2) and CXCL1 secreted by Kupffer cells (KCs), facilitating their migration along the chemotactic gradient to the site of injury. Infiltrating neutrophils exacerbate liver damage by releasing myeloperoxidase (MPO), elastase, ROS, and neutrophil extracellular traps (NETs), which directly disrupt hepatocyte structure and form microthrombi.[75–77] Research indicates that knockdown of cGAS or STING alleviates HIRI-induced inflammation and liver injury by inhibiting the cGAS-STING pathway.[78,79]

DAMPs-mediated TLR Signaling Integrates with cGAS–STING Pathway

Besides mtDNA, a spectrum of damage-associated molecular patterns (DAMPs)—including high-mobility group box 1 (HMGB1), ATP and mitochondrial formyl peptides—are released from stressed hepatocytes and activate Toll-like receptor (TLR) pathways on Kupffer cells and other innate immune cells.[80] In the early phase of hepatic reperfusion, disulfide-HMGB1 binds TLR4 and recruits the adaptor TIRAP/MyD88 to potently activate NF-κB, precipitating a rapid inflammatory burst.[81,82] Subsequent internalization of TLR4 engages the TRAM/TRIF module, leading to TBK1/IKKε-mediated phosphorylation of IRF3 and the production of IFN-I.[83–85] HMGB1 also signals through the receptor for advanced glycation end products (RAGE), reinforcing NF-κB activation and establishing an "HMGB1–TLR4/RAGE" axis that sustains hepatic inflammation.[86] Moreover, TLR2 and TLR9 are up-regulated in HIRI and signal via MyD88-dependent pathways to further enhance NF-κB-driven cytokine production.[87,88]

These TLR-dependent pathways intersect with cGAS–STING signalling at multiple nodes. Both NF-κB and IRF3 are shared effectors between the TLR and cGAS–STING cascades; IRF3 and IFN-I induced by TLR4-TRIF signalling up-regulate cGAS expression because the cGAS promoter contains interferon-stimulated response elements, making cGAS itself an interferon-stimulated gene.[89] Conversely, activated NF-κB can prolong STING signalling by disrupting the microtubule network and preventing lysosomal degradation of STING, thereby amplifying the cGAS–STING signal.[90] These findings highlight a tightly interwoven network in which DAMPs-driven TLR signalling and cGAS–STING activation converge on NF-κB and IRF3 to determine the magnitude and duration of the inflammatory response during HIRI.

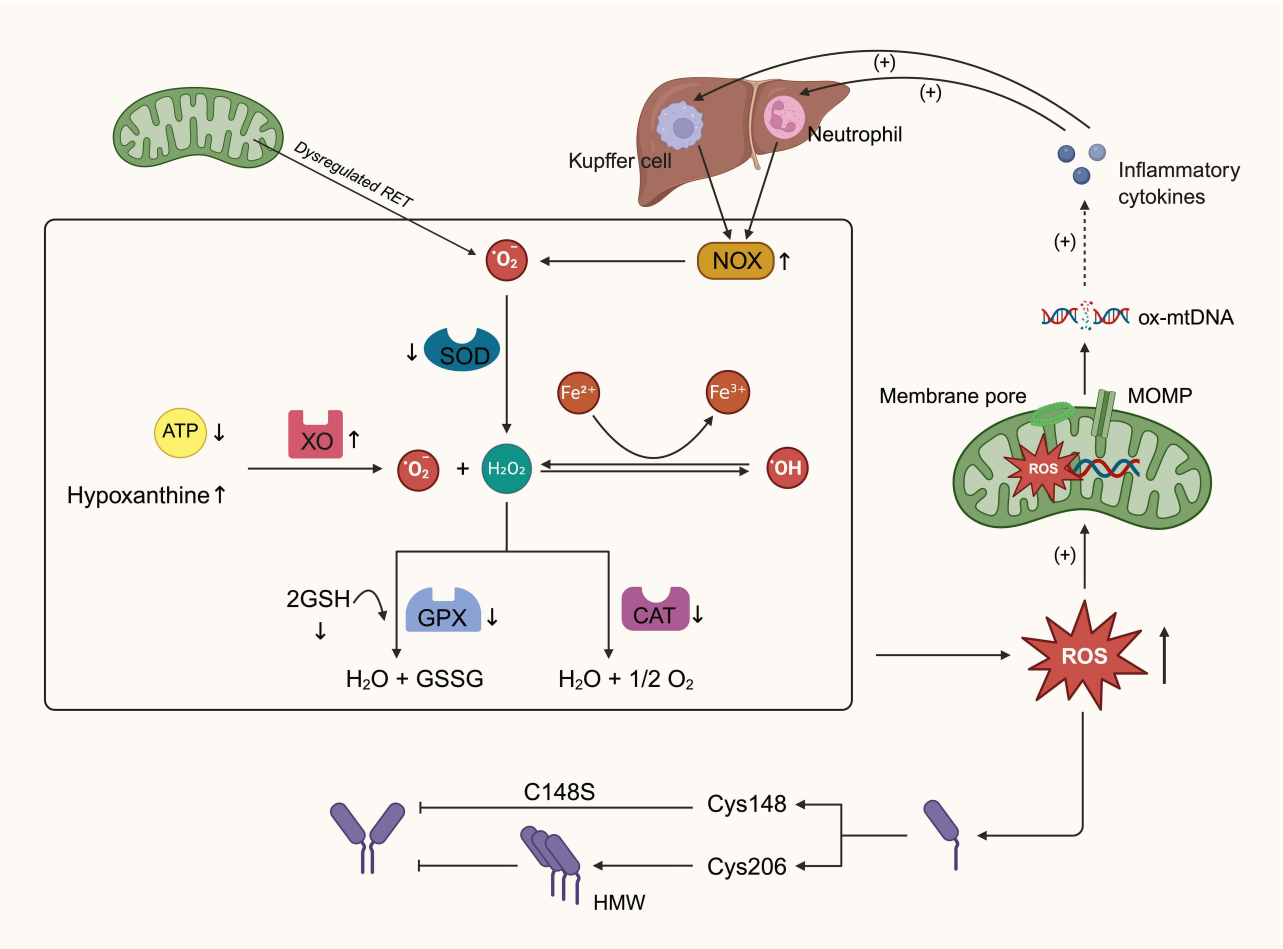

Figure 4 Oxidative Stress and cGAS-STING Pathway Bidirectional Regulation Schematic of oxidative stress–cGAS–STING crosstalk in HIRI. Dysregulated mitochondrial RET, XO, and NOX drive ROS overproduction, while reduced SOD, GPX, CAT, and GSH impair clearance. Excess ROS induce MOMP and ox-mtDNA release, activating cGAS–STING signaling. Kupffer cells and neutrophils amplify ROS and cytokines, forming a vicious cycle. Oxidation of STING Cys148/Cys206 regulates its polymerization and downstream signaling. Created with BioRender.com.

Abbreviations: RET, reverse electron transport; XO, xanthine oxidase; ROS, reactive oxygen species; SOD, superoxide dismutase; GPX, glutathione peroxidase; CAT, catalase; GSH, glutathione; MOMP, mitochondrial outer membrane permeabilization; ox-mtDNA, oxidized mitochondrial DNA; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; KCs, Kupffer cells.

Bidirectional Regulation of Oxidative Stress and cGAS-STING Pathway

Oxidative stress is one of the central mechanisms mediating tissue damage during HIRI.[91] It represents a pathological state triggered by an imbalance between ROS generation and the scavenging capacity of the endogenous antioxidant defense system, inducing oxidative damage to various biomolecules.[92] Figure 4 illustrates the bidirectional regulatory relationship between oxidative stress and the cGAS-STING pathway.

Oxidative Stress-Mediated MtDNA Damage as a Key Trigger

The aberrant release of mtDNA driven by oxidative stress serves as a primary link connecting oxidative stress to cGAS-STING activation. During ischemia-reperfusion, mitochondrial electron transport chain (ETC) dysfunction leads to excessive generation of ROS. Impaired ATP synthesis during ischemia causes abnormal electron transfer within ETC complexes. Upon reperfusion, the restoration of oxygen supply promotes increased electron leakage, primarily occurring at complexes I and III, generating superoxide anion ($\cdot O_2^-$). $\cdot O_2^-$ is converted to H_2O_2 by superoxide dismutase (SOD), and H_2O_2 further generates highly reactive hydroxyl radicals ($\cdot OH$) via the Fenton reaction.[44] These ROS preferentially attack mtDNA within the matrix, which lacks histone protection and has limited repair capacity. This induces oxidation of guanine residues to form 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG), disrupting mtDNA structural stability and

generating immunogenic ox-mtDNA.[93,94] Subsequently, ox-mtDNA lesions unrepaired by 8-oxoguanine-DNA glycosylase (OGG1) are cleaved by flap endonuclease 1 (FEN1) into 500–650 base pair (BP) mtDNA fragments. These fragments escape from the mitochondrial matrix into the cytosol through the persistently open mPTP and channels formed by VDAC oligomerization.[95,96] Additionally, BAK/BAX-mediated mitochondrial outer membrane permeabilization (MOMP) and GSDMD pyroptotic pore formation can facilitate ox-mtDNA release.[97,98] Compared to intact mtDNA, ox-mtDNA exhibits enhanced affinity for cGAS due to double-strand breaks, loosened spatial conformation, and exposure of oxidized bases, thereby more efficiently activating the cGAS-STING pathway.[99,100]

Sources of ROS and The Antioxidant Deficit

Mitochondria are the primary sites of ROS production. During the ischemic phase, hepatic hypoxia leads to mitochondrial electron transport chain dysfunction, significantly reducing ATP synthesis while accumulating substrates like hypoxanthine, which provides conditions for xanthine oxidase (XO) activation upon reperfusion. In the reperfusion phase, following the restoration of blood flow and oxygen supply, aberrant reverse electron transfer (RET) at mitochondrial complex I causes a burst release of superoxide anion ($\cdot O_2^-$). This $\cdot O_2^-$ is converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD). Subsequently, in an iron-overloaded microenvironment, H_2O_2 further generates the highly toxic hydroxyl radical ($\cdot OH$) via the Fe^2+-dependent Fenton reaction, initiating lipid peroxidation.[101–103] Concurrently, xanthine oxidase (XO) catalyzes hypoxanthine oxidation, accompanied by substantial production of $\cdot O_2^-$ and H_2O_2, constituting a major early source of ROS.[104] Furthermore, NOX2-p47phox-dependent NADPH oxidases in neutrophils and KCs are also activated during reperfusion, further promoting explosive ROS generation.[105,106]

Conversely, studies demonstrate that in HIRI, the activity of endogenous antioxidant enzymes – such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) – is significantly reduced. Additionally, the content of reduced glutathione (GSH) is diminished, weakening ROS scavenging capacity.[107,108] This dual imbalance between ROS generation and clearance ultimately leads to the predominance of oxidative stress, which mediates hepatic injury.

The Vicious Cycle of Bidirectional Regulation

It is noteworthy that oxidative stress serves not only as a direct executor of damage but also forms a bidirectional regulatory network with the cGAS-STING pathway. As described above, ROS activate cGAS through direct oxidative damage or by inducing mtDNA leakage, prompting it to initiate STING-dependent downstream signaling. Activated STING promotes the secretion of pro-inflammatory cytokines (such as TNF-α and IL-6) via the IRF3 and NF-κB pathways, recruiting large numbers of infiltrating immune cells like neutrophils and macrophages into the liver. These infiltrating immune cells further release ROS, creating a vicious cycle of oxidative stress and inflammation. Furthermore, studies have revealed that ROS can regulate STING function by oxidizing its Cys residues. Among these, Cys148 is constitutively oxidized under steady-state conditions, and its mutant (C148S) partially compromises STING activation capacity. In contrast, Cys206 is specifically oxidized following oxidative stress or ligand (cGAMP) stimulation. This oxidation drives STING to form high-molecular-weight (HMW) polymers via intermolecular disulfide bonds, hindering its conformational rearrangement. Consequently, TBK1-dependent phosphorylation at Ser366 is impeded, thereby attenuating TBK1 kinase activity and downstream IRF3 activation.[109,110] Therefore, the bidirectional interaction between oxidative stress and the cGAS-STING pathway collectively drives the pathological progression of HIRI through inflammation amplification and ROS feedback mechanisms.

cGAS-STING Pathway Modulation of Cell Death Programs

The pathological process of HIRI involves a complex and synergistically interacting regulatory network comprising multiple cell death modes, including pyroptosis, autophagy, apoptosis, and PANoptosis. The innate immune response serves as the core driver of this network, with the cGAS-STING signaling pathway emerging as an upstream central hub that transcends its classical functions. It simultaneously regulates multiple death programs through cell type-specific mechanisms, as shown in Figure 5.

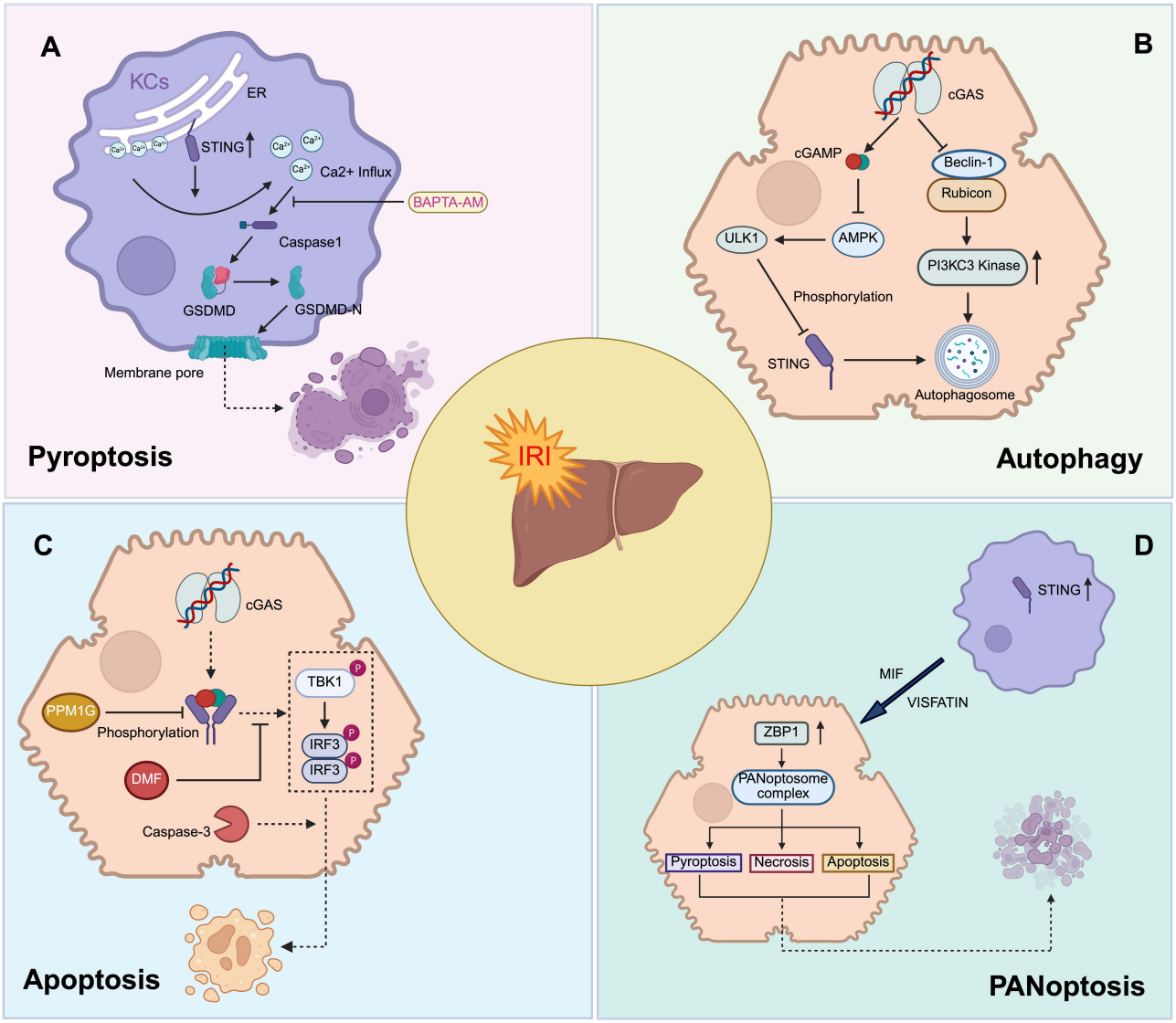

Figure 5 cGAS-STING Pathway Modulation of Cell Death Programs The cGAS–STING pathway orchestrates multiple programmed cell death modes in HIRI. (**A**) Pyroptosis: In KCs, STING induces ER Ca^2+ release and caspase-1/GSDMD activation; blocked by BAPTA-AM; (**B**) Autophagy: cGAS binds Beclin-1, releases Rubicon inhibition, enhances PI3KC3 activity, and promotes autophagosome formation; (**C**) Apoptosis: cGAS–STING activates TBK1/IRF3 and caspase-3; inhibited by PPM1G or DMF; (**D**) PANoptosis: STING-driven MIF/VISFATIN signaling activates ZBP1-PANoptosome, integrating pyroptosis, necroptosis, and apoptosis. Created with BioRender.com.
Abbreviations: KC, Kupffer cell; ER, endoplasmic reticulum; GSDMD, gasdermin D; PI3KC3, Class III phosphatidylinositol 3-kinase complexes.

Pyroptosis

Pyroptosis, a lytic pro-inflammatory type of cell death, is one of the key pathological processes in HIRI.[111,112] In HIRI, ischemia-reperfusion stimulation primarily triggers NLRP3 inflammasome assembly through the release of DAMPs, such as ATP, mtDNA, HMGB1, and Cathepsin B. This activates the caspase-1/GSDMD axis, inducing pyroptosis.[113] Additionally, the non-canonical pyroptosis pathway (such as Caspase-11-mediated pyroptosis) also contributes to HIRI. Studies have confirmed that ghrelin and isoflurane ameliorate non-canonical pyroptosis pathway-mediated liver injury by suppressing the Caspase-11/GSDMD pathway.[114–116]

Pyroptosis exhibits significant cell type specificity in HIRI, being primarily confined to KCs and bone marrow-derived innate immune cells.[117,118] While hepatocytes are generally resistant to this process, emerging evidence indicates that under certain pathological conditions, hepatocytes can also undergo pyroptosis. For instance, diabetes promotes oxidative stress-mediated NLRP3 inflammasome activation in hepatocytes during HIRI, leading to their pyroptosis.[119]

However, exosomes derived from adipose-derived mesenchymal stem cells (ADSCs-Exo) have been shown to attenuate pyroptosis and promote regeneration in injured liver.[120] Furthermore, recent studies demonstrate that PTX3 exacerbates hepatocyte pyroptosis in HIRI by promoting macrophage M1 polarization, further highlighting the complex regulatory mechanisms of pyroptosis across different cell types in HIRI.[121]

Studies demonstrated that endogenous high mobility group box 1 (HMGB1) promoted the assembly and activation of the NLRP3 inflammasome within KCs, leading to caspase-1/GSDMD-dependent pyroptosis. Glycyrrhizin effectively blocks this pyroptotic pathway by directly binding to and inhibiting HMGB1 function, thereby mitigating liver injury.[122] Furthermore, studies have confirmed that Oridonin alleviated HIRI by suppressing KC pyroptosis mediated through the PKM2/NLRP3 pathway.[123] These findings underscore the central role of KCs in regulating pyroptosis.

Research has revealed that STING signaling can mediate macrophage pyroptosis by regulating calcium-dependent pathways. In HIRI, STING expression is upregulated in KCs, triggering endoplasmic reticulum calcium release and causing a significant increase in intracellular calcium concentration.[124] This calcium overload promotes the activation of caspase-1/GSDMD-mediated pyroptosis. Notably, this process can be effectively suppressed by BAPTA-AM, a cell-permeable calcium chelator.[125]

Autophagy

The role of autophagy in HIRI is dualistic and mechanistically complex. On one hand, autophagy serves a essential protective function by selectively clearing damaged organelles and maintaining cellular homeostasis. A central mechanism in this process is mitophagy, which relies on the PINK1/Parkin signaling axis to identify and eliminate dysfunctional mitochondria, thereby reducing ROS accumulation and inhibiting apoptosis.[126–128] Autophagy can supports mitochondrial function through the SIRT1-dependent pathway, where SIRT1-mediated deacetylation enhances autophagic activity, attenuates liver injury, and confers protection through anti-inflammatory and anti-apoptotic effects.[129] Additionally, the transcription factor KLF6 suppresses Beclin1 transcription through direct promoter binding and facilitates inhibitory phosphorylation of ULK1 (Ser757) via mTOR pathway activation, thereby exerting dual control over autophagy initiation. This restraint on excessive autophagic activation helps alleviate hepatocyte damage.[130]

Intriguingly, autophagy in liver sinusoidal endothelial cells (LSECs) serves as a critical protective mechanism during HIRI by modulating inflammatory responses through dual pathways. On one hand, autophagy activation upregulates the Kruppel-like factor 2 (KLF2)–endothelial nitric oxide synthase (eNOS) axis, enhancing nitric oxide (NO) production.[131] This not only ameliorates hepatic sinusoidal vasoconstriction and microvascular dysfunction but also suppresses neutrophil adhesion and platelet aggregation.[132] On the other hand, autophagy selectively removes organelles damaged by oxidative stress, thereby maintaining cellular integrity and preventing the release of DAMPs.[133] This process indirectly attenuates KCs activation and the subsequent secretion of pro-inflammatory cytokines, further mitigating sterile inflammation.[134]

While moderate autophagy exerts a protective role by maintaining mitochondrial homeostasis, its excessive activation or functional deficiency can either exacerbate HIRI.[135] In HIRI, when autophagy is functionally impaired, key components of the mitochondrial respiratory chain (such as COX IV, SDHB) are reduced, accompanied by a decline in the mitochondrial membrane potential (MMP). Meanwhile, the release of pro-inflammatory cytokines increases, expression of pro-apoptotic proteins (such as Bax and activated caspase-3) is upregulated, and the anti-apoptotic protein Bcl-2 is downregulated—collectively indicating aggravated liver injury.[136,137] Conversely, JNK pathway-mediated overactivation of autophagy upregulates interferon regulatory factor 1 (IRF-1), which in turn induces Beclin1 expression and leads to dysregulated mitophagy.[138,139] This dysregulation initiates a dual pathogenic cascade: it accelerates ATP depletion, culminating in an energy crisis, while concurrently promoting Caspase-3 cleavage and activation. The synergy between these processes amplifies apoptotic signaling and culminates in autophagic cell death.[140]

In HIRI, a close bidirectional regulatory relationship exists between autophagy and the cGAS–STING signaling pathway. Beyond the well-established mechanism by which mitophagy clears damaged mitochondria and reduces mtDNA release, thereby suppressing cGAS activation, cGAS can also directly regulate the autophagic process through both STING-dependent and STING-independent mechanisms. Notably, although hepatocytes do not express STING, cGAS can still induce protective autophagy in a STING-independent manner.[141,142] Studies have shown that cGAS

directly binds to the coiled-coil domain (CCD) of Beclin-1, a core autophagy-related protein. This interaction competitively inhibits the binding of the autophagy negative regulator Rubicon to Beclin-1, thereby relieving Rubicon-mediated suppression of the Class III phosphatidylinositol 3-kinase complexes (PI3KC3). As a result, PI3KC3 kinase activity is enhanced, promoting autophagosome formation.[143] This mechanism facilitates the timely clearance of damaged mitochondria and inhibits apoptosis, contributing to a protective effect in HIRI.

On the other hand, the second messenger cGAMP, produced by cGAS, not only activates the STING pathway but also participates in a negative feedback loop that modulates autophagy.[144] cGAMP inhibits AMPK activity, which relieves AMPK-mediated suppression of ULK1 kinase, leading to ULK1 activation. Activated ULK1 subsequently phosphorylates STING at serine 366 (S366). This phosphorylation event selectively inhibits the STING–TBK1–IRF3 signaling axis, reduces the production of inflammatory factors such as IFN-I, and promotes STING degradation, thereby facilitating the timely termination of inflammatory signaling and preventing excessive immune activation.

Additionally, single-cell sequencing analysis revealed that the cGAS-STING pathway in liver endothelial cells is closely associated with the mitophagy-related genes (MRGs). Endothelial cells with high MRGs score exhibited active mitophagy and engaged in significant interaction with monocytes via the macrophage migrationinhibitory factor (MIF) pathway. In contrast, low MRGs score endothelial cells demonstrated insufficient autophagic capacity, and their intercellular communication depended on the cGAS-STING pathway. This suggests that cGAS-STING may participate in remodeling the immune microenvironment of HIRI by regulating mitophagy in endothelial cells.[145]

Apoptosis

In HIRI, apoptosis is one of the major forms of hepatocyte death.[146] This process is tightly regulated and primarily mediated by the activation of caspase protease family members.[147] Within the context of HIRI, apoptosis is mainly coordinated through three interrelated signaling pathways: the mitochondrial pathway, which acts as the central route and is triggered by oxidative stress and calcium overload, leading to increased mitochondrial membrane permeability, release of cytochrome c and other pro-apoptotic factors, and subsequent activation of caspase-9;[148] the death receptor pathway, initiated by death signals such as Fas ligand or TNF-α released from immune cells during reperfusion, which binds to corresponding death receptors on hepatocytes and recruits and activates caspase-8;[149,150] and the endoplasmic reticulum (ER) stress pathway, mainly induced by disruption of calcium homeostasis and accumulation of unfolded proteins. Excessive ER stress activates transcription factors such as CHOP, which in turn regulates the expression of apoptosis-related proteins like Bcl-2 and Bax.[151,152] These three pathways ultimately converge on the activation of the key executioner molecule, caspase-3, thereby triggering programmed hepatocyte death.

Recent studies have revealed a close association between apoptosis and the cGAS–STING signaling pathway. For instance, studies using myeloid cell-specific STING knockout mouse models have demonstrated that loss of STING markedly alleviates apoptosis after hepatic ischemia-reperfusion.[153] Additionly, protein phosphatase Mg^2+/Mn^2+-dependent 1G (PPM1G) directly binds to STING and promotes its dephosphorylation, thereby inhibiting STING pathway activation and significantly attenuating hepatocyte apoptosis in HIRI.[154] Dimethyl fumarate (DMF), an immunomodulatory agent, interferes with the interaction between STING and TBK1 or IRF3, disrupting the assembly of the STING signalosome and downstream inflammatory signaling, Mitophagythereby exerting an anti-apoptotic effect in a STING-dependent manner.[155] These studies further supporting the critical role of the STING pathway in regulating HIRI-related apoptosis.

PANoptosis

PANoptosis is an inflammatory and lytic mode of programmed cell death regulated by the PANoptosome complex, distinguished by its unique integration of key molecular features from pyroptosis, apoptosis, and necroptosis.[156,157] The core mechanism driving this process involves the assembly of the PANoptosome complex, mediated by sensors such as ZBP1, which leads to the coordinated activation of multiple cell death pathways, resulting in marked inflammatory responses and tissue damage.[158] In HIRI, STING has been identified as a critical upstream regulator of PANoptosis, and its activation significantly promotes the initiation and progression of PANoptosis.[159] Macrophages play a central role in this process: upon activation, they not only exhibit elevated STING expression but also amplify and transmit pro-death

signals to hepatocytes via intercellular communication, thereby inducing PANoptosis in hepatocytes. Bioinformatic analyses further suggest enhanced communication between macrophages and hepatocytes through MIF and VISFATIN signaling pathways during HIRI, indicating that these factors may play important roles in mediating such pro-inflammatory intercellular crosstalk.[160]

Therapeutic Strategies Targeting cGAS–STING Pathway

According to the findings, the cGAS-STING pathway has been identified as the central mediator of aseptic inflammation, oxidative stress and cell death in HIRI. Therefore, therapeutic strategies targeting key nodes of this pathway and mitochondrial protection have emerged as research directions for modulating disease progression.

Inhibitors of Cytoplasmic DNA

The initiation of the cGAS-STING pathway depends on the presence of cytoplasmic DNA, which mainly results from the release of mtDNA during HIRI. Reducing the availability of these ligands is one of the main intervention strategies. Table 1 summarizes the various Cytoplasmic DNA inhibitors found in the literature. On the one hand, certain inhibitors such as the antimalarial drugs Hydroxychloroquine and Quinacrine may not be ideal therapeutic options for HIRI due to their potential cytotoxicity and immunosuppressive risks. However, in patients with hepatic ischemia accompanied by

Table 1 Inhibitors of cGAS–STING Pathway

Target	Drug	Mechanism	References
Cytoplasmic DNA	Hydroxychloroquine	Binding to the DNA binding domain of cGAS and replacing the bound DNA	[161]
	Quinacrine	Binding to the DNA binding domain of cGAS	[161]
	X6	Binding to DNA at the cGAS-DNA interface	[162]
	Suramin	As a nucleic acid mimetic to competitively displace DNA from the cGAS DNA-binding site	[163]
cGAS	RU.521	Binding to the cGAS active spot to reduce affinity for ATP and GTP	[164]
	PF-06928215	Binding to the cGAS active spot to block ATP and GTP access	[165]
	G108/G150	Taking over cGAS's active spot to hinder ATP/GTP binding	[166]
	Aspirin	Acetylating cGAS at lysine residues (K384/K394/K414)	[167]
	CU-32/CU-76	Disrupting cGAS dimerization	[168]
	S2/S3	Taking over cGAS's active spot to hinder ATP/GTP binding	[169]
	Perillaldehyde	Inhibition of cGAS activity	[170]
	Epigallocatechin gallate	Targeting G3BP1 to disrupt cGAS's primary condensation state	[171]
	4-Sulfonic calix[6] arene	Inhibiting cGAS by sulfonate-mediated blockade of the DNA-binding site	[172]
	XQ2B	Binding to the DNA-binding site of cGAS to block dsDNA interaction and subsequent phase separation	[173]
	Compound 3	Covalently binding to Cys419 of cGAS to block substrate access to the catalytic pocket	[174]
STING	C-178/C-176/ C-170/C-171	Covalently binding to Cys91 of STING to block its palmitoylation	[175]
	H-151	Covalently binding to Cys91 of STING to block its palmitoylation	[175]
	NO_2-FAs	Blocking STING protein activation-induced palmitoylation	[176]

(*Continued*)

Table 1 (Continued).

Target	Drug	Mechanism	References
	Astin C	Preventing the recruitment of IRF3 to STING	[177]
	Compound 18	Binding to the open inactive conformation of the STING homodimer	[178]
	SN-011	Binding to the STING cyclic dinucleotide-binding pocket to lock the dimer in an open inactive conformation	[179]
	ISD-017	Blocking STING's translocation from the endoplasmic reticulum to the Golgi apparatus	[180]
	Degrader 2	Simultaneously binding to Cys91 of STING and RNF126 E3 ligase, inducing targeted ubiquitin-proteasomal degradation	[181]

autoimmune diseases such as systemic lupus erythematosus, these drugs may still offer some therapeutic benefits. It is worth noting that novel derivatives like X6 have demonstrated more effective inhibition of cGAS in preclinical studies compared to traditional antimalarials, yet their specific application in HIRI requires further evaluation to balance efficacy and safety.

Inhibitors of cGAS

Direct inhibition of cGAS prevents the synthesis of the second messenger cGAMP, thereby interrupting downstream STING signaling. Table 1 summarizes the literature on cGAS inhibitors. However, some cGAS inhibitors are not ideal candidates for the treatment of HIRI. Specifically, although PF-06928215 exhibited high binding affinity for cGAS and demonstrates micromolar (μM) inhibition in vitro, it failed to downregulate DNA-induced interferon-beta (IFN-β) production in cellular models. This suggests that its limited cell permeability, potential competition with intracellular nucleotides, or unfavorable pharmacokinetic properties may hinder its translational potential. Furthermore, while the natural compound perillaldehyde was shown to inhibit cGAS, its concomitant suppression of antiviral defense mechanisms necessitates careful consideration of the risk-benefit ratio within the perioperative context.

Inhibitors of STING

As a key molecule in the cGAS-STING pathway, it is crucial to search for STING inhibitors. Table 1 compiles a list of cGAS inhibitors documented in the literature. Studies demonstrated that STING inhibitors significantly suppress palmitoylation, a modification that is essential for the activation of its downstream effector TBK1/IRF3.[182] Hence, the administration timing of STING inhibitors is also of great importance.

Mitochondrial Stabilization Strategies

Mitochondrial damage-induced release of mtDNA serves as a key trigger for activating the cGAS–STING signaling pathway. Consequently, stabilizing mitochondrial structure and function to prevent aberrant mtDNA leakage has emerged as a crucial therapeutic strategy. Multiple pharmacological and biological interventions have shown promise by targeting distinct aspects of mitochondrial dysfunction:

Inhibition of mPTP Opening

The mPTP inhibitor Cyclosporine A (CsA) maintains the integrity of the mitochondrial inner membrane by inhibiting CYPD-dependent mPTP opening.[183] This action attenuates mitochondrial matrix swelling and outer membrane rupture, effectively reducing mtDNA release into the cytosol.[184,185]

Inhibition of VDAC Oligomerization

Pharmacological inhibitors of VDAC oligomerization such as VBIT-4 directly inhibit VDAC oligomerization, hindering the formation of high-conductance pores in the outer mitochondrial membrane that facilitate mtDNA efflux.[186]

Modulation of Mitochondrial Dynamics

Rebalancing mitochondrial fission and fusion represents another viable approach to attenuate pathological mtDNA leakage. For instance, exercise-induced secretion of the myokine Irisin attenuates Drp1-mediated mitochondrial fission.[187] Similarly, adipose-derived mesenchymal stem cell exosomes (ADSC-exos) demonstrate the ability to upregulate fusion proteins (MFN1, MFN2, OPA1) and downregulate fission regulators (Drp1, Fis1), thereby promoting mitochondrial integrity.[188]

Enhancement of Mitophagy and Antioxidant Defense

The Nrf2 activator CDDO-imidazolide (CDDO-Im) accelerates the clearance of damaged mitochondria via enhanced mitophagy and reduces oxidative stress, thereby decreasing both ROS production and mtDNA release.[189]

These mitochondrial protection strategies effectively reduce the primary triggers of cGAS-STING pathway activation by preserving mitochondrial integrity, offering a therapeutic direction for ameliorating HIRI.

Conclusion and Future Perspectives

In HIRI, the cGAS-STING pathway serves as a central hub linking mitochondrial dysfunction to inflammatory cascades by sensing cytosolic mtDNA. Notably, LSECs—early and vulnerable targets in HIRI—may play a significant role in the release of DAMPs, including mtDNA. Although mtDNA-triggered cGAS-STING activation is conserved in endothelial cells across multiple organs (such as retina, heart, lungs),[190–192] direct evidence in LSECs during HIRI remains limited and warrants further investigation.

This pathway amplifies tissue damage through TBK1–IRF3/NF-κB-driven expression of pro-inflammatory cytokines and IFN-I, exacerbating neutrophil infiltration, macrophage pyroptosis, and hepatocyte apoptosis. Its role is highly cell-type specific: in STING-negative hepatocytes, cGAS activation promotes protective autophagy, whereas in macrophages and endothelial cells, STING activation exacerbates inflammation via NLRP3 activation, calcium dysregulation, and impaired mitophagy. Furthermore, the pathway exhibits spatiotemporal dynamics across different phases of HIRI, influenced by oxidative stress, immune infiltration, and DAMPs release.

Despite these advances, several challenges remain. The structural basis of ox-mtDNA recognition by cGAS and the precise regulation of mitophagy require further investigation. Cellular crosstalk—particularly among hepatocytes, macrophages, and endothelial cells—warrants deeper exploration using single-cell spatial omics to decipher microenvironment-specific signaling. Translationally, current inhibitors of cGAS-STING and mitochondrial protectants suffer from off-target effects and delivery limitations. Nanocarriers and gene-editing tools may enable more precise intervention.[193] Moreover, interactions with other cell death pathways such as ferroptosis and necroptosis remain underexplored.

Future studies should specifically examine whether preserving mitochondrial integrity in LSECs can attenuate cGAS-STING activation and improve outcomes, offering a novel therapeutic angle for mitigating sterile inflammation in HIRI.

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The authors declare no conflicts of interest that pertain to this work.

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