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REVIEW

cGAS-STING Targeting Offers Novel Therapeutic Opportunities in Liver Diseases

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Abstract: Cyclic GMP/AMP (cGAMP) synthase (cGAS), coupled with the endoplasmic reticulum (ER)-anchored adaptor protein stimulator of interferon genes (STING), constitute key components of the type 1 interferon signaling network. cGAS detects both pathogen-derived DNA and aberrant cytosolic self-DNA, establishing the cGAS-STING pathway as a central player in autoimmune disorders, sterile inflammation, and senescence-related processes. However, sustained abnormal activation of this signaling axis is implicated in the pathogenesis of chronic inflammatory and autoimmune conditions. Recent studies have uncovered the pivotal role of cGAS-STING signaling in driving inflammation-associated pathologies, particularly hepatic disorders. Advances in understanding the molecular dynamics of this pathway have facilitated the development of targeted small-molecule inhibitors with therapeutic potential for cGAS-STING-driven liver diseases. In this review, we first delineate the core architecture of the cGAS-STING signaling cascade. Building on this framework, we analyze emerging evidence elucidating the mechanistic contributions of cGAS-STING activation to hepatic pathophysiology. Subsequently, we catalog pharmacologically active compounds capable of modulating this pathway in liver disease models. Finally, we critically evaluate current challenges in translating cGAS-STING-targeted therapies and propose strategic approaches to address these limitations. This synthesis underscores innovative therapeutic opportunities arising from precision modulation of the cGAS-STING axis in liver diseases.

Keywords: cGAS, STING, antagonist, liver diseases

Introduction

Cyclic GMP/AMP (cGAMP) synthase (cGAS), in conjunction with the endoplasmic reticulum (ER)-localized adaptor stimulator of interferon genes (STING), serves as core components of innate immunity.[1–3] Pathogen-derived DNA acts as a prototypical pathogen-associated molecular pattern (PAMP), providing the essential molecular stimulus for cGAS activation.[1,2] Upon DNA recognition, cGAS catalyzes the production of cGAMP, which subsequently engages STING, triggering its ER-to-Golgi translocation. This spatial redistribution enables STING to recruit and activate TANK-binding kinase 1 (TBK1) and interferon regulatory factor 3 (IRF3), ultimately driving IRF3 phosphorylation, dimerization, and nuclear translocation to orchestrate type I interferon (IFN-I) and IFN-stimulated gene (ISG) expression.[2,4,5]

Emerging data indicate that dysregulated activation of the cGAS-STING pathway induces pathological consequences, including neuroinflammatory cascades and neurodegenerative progression, exacerbating neurological disorders.[1,2,4,6–9] Over the last decade, scientific focus has shifted toward deciphering the hepatic implications of this pathway.[10,11] The central involvement of cGAS-STING signaling in disease pathogenesis has propelled the development of pharmacological modulators targeting this axis, positioning it as a promising therapeutic frontier for precision medicine.[12–15]

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In this review, the core architecture of the cGAS-STING signaling cascade was first delineated. We then provide mechanistic insights into its pathogenic role in hepatobiliary disorders and discuss recent research that highlights pathomechanistic evidence by which cGAS-STING contributes to hepatic pathologies. Then, we summarize a list of pharmacologically active modulators, which modulate the cGAS-STING axis in hepatic pathologies. Finally, we discuss translational challenges of this new proposed therapeutic approach and provide strategic solutions for clinical translation.

Overview of the cGAS-STING Axis

Functioning upstream of STING,[16,17] cyclic GMP/AMP synthase (cGAS) serves as the DNA-sensing nucleotidyltransferase that initiates innate immune responses against pathogenic extranuclear DNA through the cGAS-STING signaling axis.[18] This evolutionarily conserved system not only mediates antimicrobial defense but also coordinates sterile inflammation, autoimmunity, and cellular senescence via detection of endogenous DNA (including mitochondrial DNA leaks and genotoxic stress-induced chromatin fragments).[18] Structurally classified as a nucleotidyl transferase (NTase), cGAS (gene symbol MB21D1) exhibits sequence-independent binding to microbial dsDNA (viral, bacterial, or protozoan).[18] STING (also termed ERIS,[19] MPYS,[20,21] MITA,[22] or TMEM173[18]) is a 40-kDa ER-resident adaptor protein that orchestrates downstream signaling (Figure 1). Mechanistically, cGAS activation occurs through three principal routes, ie detection of exogenous microbial dsDNA, recognition of endogenous nuclear/mitochondrial DNA leaks, and response to genotoxic stress-induced chromatin fragments.[18] Following DNA binding, cGAS undergoes structural rearrangement to catalytically synthesize 2′,3′-cyclic GMP-AMP (cGAMP) from ATP and GTP.[17,23–27] This catalytic process establishes a fundamental DNA surveillance system in mammalian cells. The second messenger cGAMP subsequently binds STING, triggering its oligomerization into functional homomeric complexes.[28,29] Subsequent structural reorganization drives STING translocation from the ER to the Golgi apparatus, where it recruits TBK1 and IKK kinases to activate dual signaling branches:[18] TBK1-mediated phosphorylation of IRF3 promotes its nuclear translocation and transcriptional activation of type I interferons (eg, IFNβ); IKK-dependent phosphorylation of IκBα liberates NF-κB for nuclear entry and upregulation of proinflammatory cytokines (TNF, IL-6).[20,21] Post-activation, STING undergoes lysosomal degradation to terminate signaling.[18] Beyond antiviral defense, the cGAS-STING axis regulates diverse cellular processes (protein synthesis, autophagy, senescence, metabolism, programmed cell death) through tight spatiotemporal control via transcriptional, posttranslational, and degradation mechanisms.[18] Physiologically, this pathway maintains tissue homeostasis; dysregulation, however, drives pathogenesis of autoimmune disorders, chronic inflammation, degenerative diseases, and cancer.[18] For detailed regulatory mechanisms, we direct readers to specialized reviews.[18]

Road to Discovery of cGAS-STING: A Historical Perspective

The research history of the cGAS-STING DNA-sensing pathway originates from early investigations into innate antiviral immunity. In 1937, the phenomenon of "virus interference" was first described, whereby monkeys infected with one virus exhibited antibody-independent protection against another virus.[30] This foundational observation laid the groundwork for a landmark discovery in 1957: Isaacs and Lindenmann demonstrated that cells exposed to inactivated influenza virus produced a soluble mediator capable of conferring viral resistance to uninfected cells.[31] They termed this mediator "interferon" (IFN) due to its ability to impede viral replication.[32,33] Subsequent studies revealed that IFN induction could be triggered not only by intact viruses but also by nucleic acids from uninfected cells, suggesting foreign nucleic acids as key immunostimulatory molecules.[30] Modern understanding recognizes type I IFNs as a cytokine family critical for antiviral responses.[34] By the late 1980s, the transcriptional regulation of cytokines had been elucidated with the discovery of NF-κB.[35] Concurrently, the interferon regulatory factor (IRF) family emerged as specialized transcription factors mediating IFN production.[36,37] Two central mechanisms of antiviral defense were established: IFN induction via the TBK1-IRF3 axis and NF-κB activation.[38] However, the cytosolic nucleic acid sensors remained enigmatic. While Toll-like receptors (TLRs) were known membrane-bound detectors, their restricted expression in immune cells failed to explain IFN production in all nucleated cells.[38] This paradox fueled the search for ubiquitously expressed cytosolic sensors.

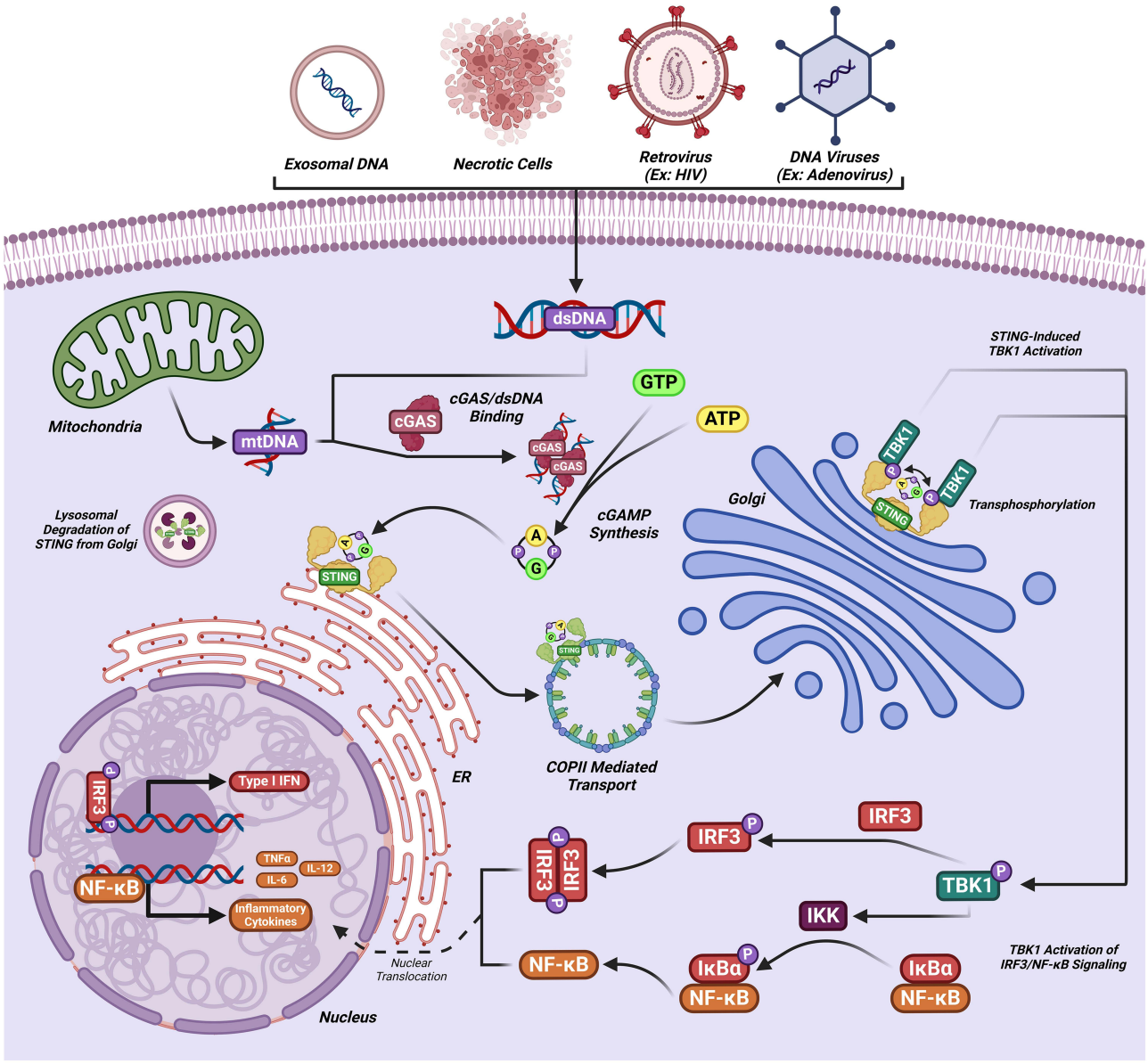

Figure 1 The cGAS-STING signaling cascade. Exogenous or endogenous double-stranded DNA (dsDNA) engages cGAS, triggering enzymatic production of cyclic GMP-AMP (cGAMP). The cGAMP-STING complex undergoes retrograde trafficking toward the Golgi apparatus, where it orchestrates TANK-binding kinase 1 (TBK1) autophosphorylation.Activated TBK1 exerts dual regulatory functions: phosphorylating interferon regulatory factor 3 (IRF3) to drive type I interferon (IFN-I) expression; activating IκB kinase (IKK) to stimulate NF-κB-dependent proinflammatory cytokine production.Terminally, STING is recycled from the Golgi and subjected to lysosomal degradation.

A breakthrough occurred in 2004–2005 with the identification of cytosolic RNA sensors melanoma differentiation-associated gene 5 (MDA5) and retinoic acid-inducible gene I (RIG-I),[39,40] and their downstream adaptor mitochondrial antiviral signaling (MAVS),[41–44] collectively forming the RIG-I-MAVS RNA detection pathway. These pattern recognition receptors (PRRs) distinguish viral RNA through structural motifs absent in host RNA, activating IFN-mediated immunity.[45] Nevertheless, cytosolic DNA sensors remained unidentified until 2006, when transfected double-stranded DNA (dsDNA) was shown to induce type I IFN independently of TLRs.[46,47] The critical missing link was resolved in 2008 with STING identification as the central adaptor for cytosolic DNA signaling[22,48](Figure 2). Early studies erroneously proposed STING (initially named MPYS) as a transmembrane protein involved in MHC II signaling and apoptosis,[21] but subsequent structural analyses confirmed its endoplasmic reticulum (ER) residency with a cytosolic-facing C-terminus.[19,48] While STING was proven essential for TBK1-IRF3-dependent antiviral responses, its upstream

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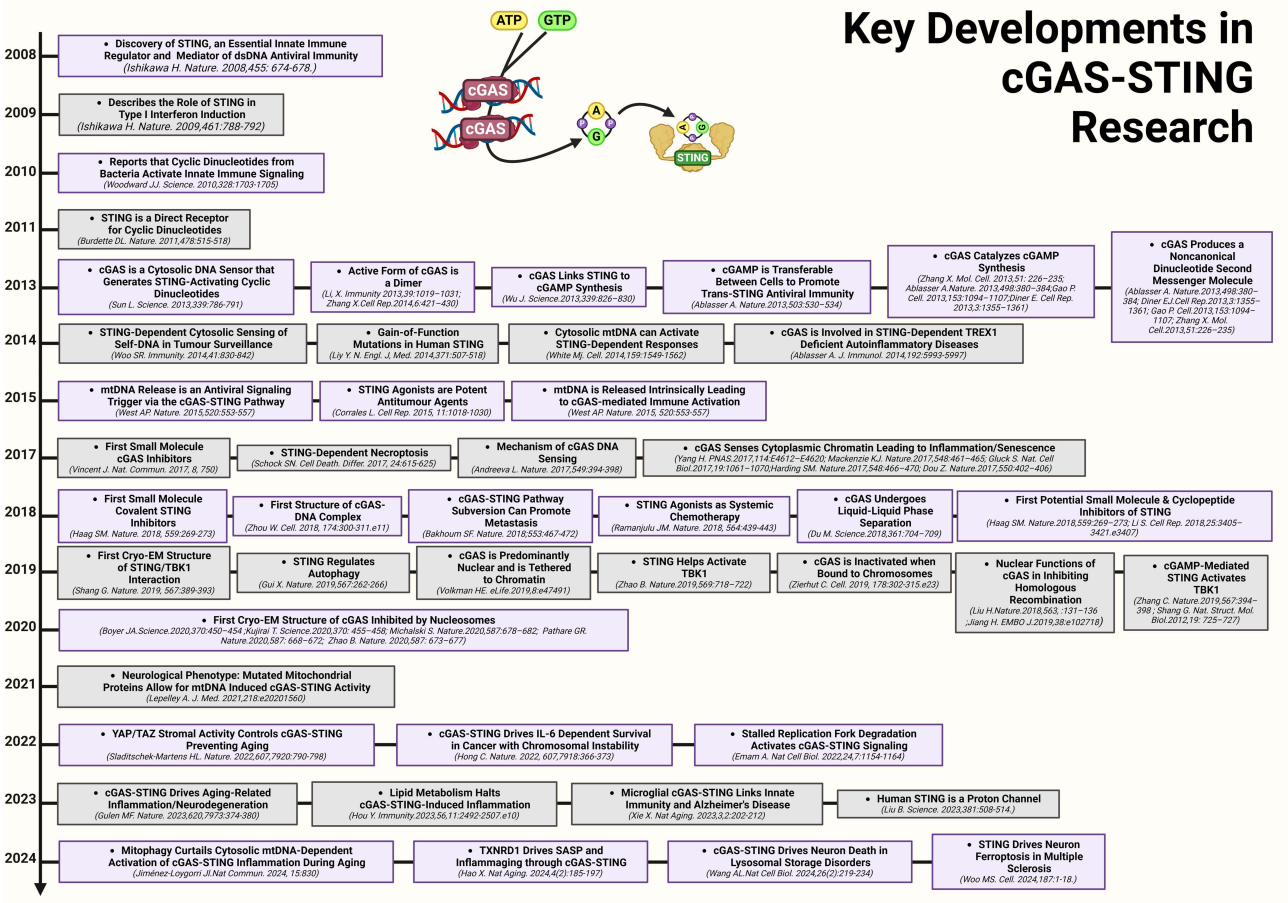

Figure 2 Key developments in cGAS-STING research. Timeline depicting the major discoveries and advances of the cGAS-STING pathway from 2008 to 2024.

DNA-sensing mechanism remained unresolved. Initial hypotheses posited STING as a direct DNA detector, supported by its responsiveness to synthetic double-stranded DNA (dsDNA) and DNA viruses.[22,48] However, AT-rich dsDNA and dsRNA were later found to activate RIG-I/MDA5 pathways independently of STING.[49] This paradox was clarified through two key discoveries: (1) STING functions as a receptor for bacterial cyclic dinucleotides,[50] and (2) cGAS was identified as the primary DNA sensor that synthesizes cGAMP to activate STING.[16,17] This cGAS-STING axis now represents the definitive pathway linking cytosolic DNA detection to innate immunity. For comprehensive historical perspectives, we direct readers to recent reviews.[2,31,51]

The Role of the cGAS-STING Axis in Liver Diseases

Acute Liver Injury

Mounting experimental evidence implicates that cGAS-STING axis activity is involved in the pathogenesis of acute liver injury caused by liver I/R injury,[52–55] CCl_4,[56] acetaminophen,[57–63] thioacetamide,[64] radiation,[65,66] concanavalin A,[67] and triptolide.[68] CCl_4-triggered ERS indices STING-mediated phosphorylation of TBK1, further phosphorylating IRF3. IRF3 combines with BAX in the mitochondria through its BH3-only domain, activating the pro-apoptotic caspase-3 and from such hepatocyte apoptosis. After persistent CCl_4 administration, hepatocyte apoptosis seen with secondary necrosis, which produces liver fibrosis.[56] Thus, these results identify that ERS-induced hepatocellular death pathways promote liver injury and fibrosis via STING.[56]

cGAS-STING axis activation contributes to acetaminophen-induced liver injury. Loss of STING prevents acetaminophen-induced acute liver injury by preventing NLRP3 activation (Figure 3).[69] As a crucial component of the sorting and assembly machinery (SAM) complex, Sam50 is needed in connecting the mitochondrial outer-membrane and inner-

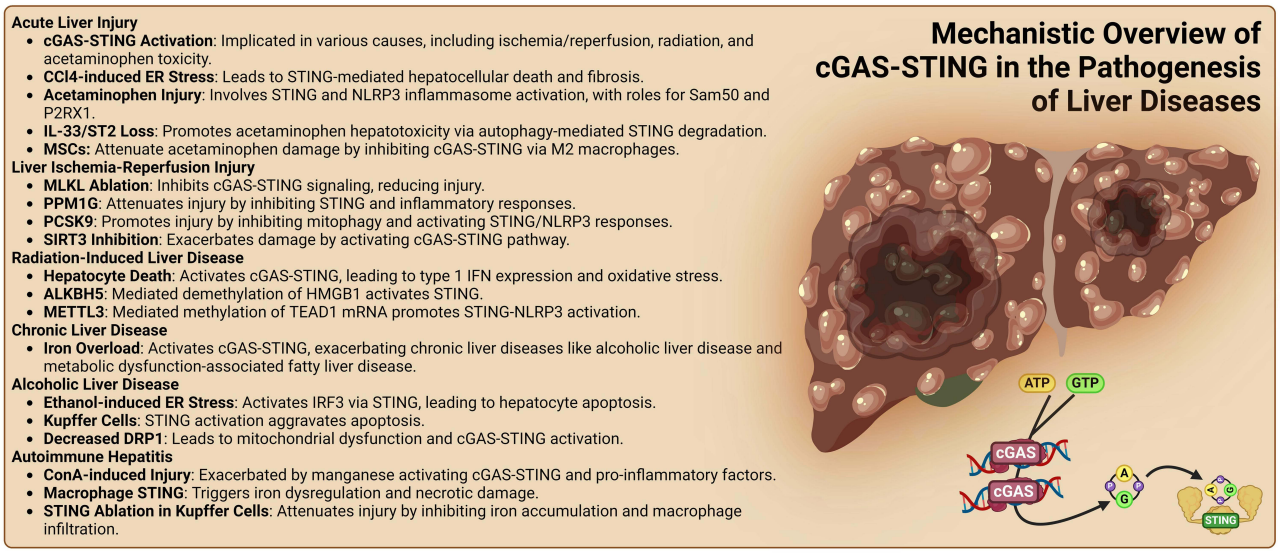

Figure 3 Overview of cGAS-STING in the pathogenesis of liver diseases. cGAS-STING is involved in the pathogenesis of acute liver injury, liver ischemia-reperfusion injury, radiation-induced liver disease, chronic liver disease, alcoholic liver disease, metabolic dysfunction-associated fatty liver disease, liver fibrosis and autoimmune Hepatitis.

membrane. Sam50 was found to contribute to acetaminophen-induced liver injury.[70] Sam50 interacts with ATPase family AAA domain-containing protein 3 (ATAD3) and mitochondrial contact site and cristae organizing system (MICOS) to maintain the stability of mtDNA. Sam50 knockout induces mtDNA aggregation. Sam50 collaborates with Mic60 to bind cardiolipin, further maintaining mitochondrial membrane integrity. Sam50 knockout promotes the externalization of cardiolipin, triggering Bax mitochondrial recruitment, mtDNA aggregation, and release. In physiological conditions, acetaminophen downregulates Sam50, while Sam50 liver-specific knockout promotes mtDNA release, activating hepatic cGAS-STING hepatic inflammation in mice. Sam50 overexpression incredibly attenuates acetaminophen-induced liver hepatoxicity.[70] Elevated purinergic receptor P2X 1 (P2RX1) was found in DILI patients and acetaminophen-induced mice.[62] Loss of P2rx1 inhibits acetaminophen-induced liver injury by inhibiting cytotoxicity and inflammation via inhibition of STING-TBK1-P65 signaling pathways.[62] STING strongly potentiates liver injury in acetaminophen-induced P2rx1-/- mice.[62] Loss of IL-33/ST2 promotes massive DNA accumulation, type 1 IFN production, and hepatotoxicity by facilitating autophagy-mediated degradation of STING in acetaminophen-induced mice.[60] Loss of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) in macrophage alleviates acetaminophen-induced liver damage, reduces proinflammatory mediators, and macrophage/neutrophil trafficking. Ablation of PTEN in macrophages reduces acetaminophen-triggered ROS and necroptosis in hepatocyte through inhibiting STING-mediated inflammatory responses via NICD and NRF2 crosstalk.[61]

Human mesenchymal stem cells (hMSCs) attenuates APAP induced-liver damage in mice through activating M2 polarization macrophages, assisting in the production of SGs, which inhibits the cGAS/STING axis and reduces macrophages-induced hepatocyte damage.[71]

New data suggests that the cGAS-STING axis is involved in the pathogenesis of sepsis-associated liver injury (Figure 4). Increased activated XBP1 was observed in hepatocytes in LPS-induced sepsis-associated liver injury mice. Hepatocyte-specific XBP1 knockout aggravates liver injury through increasing pyroptosis and enhancing macrophage STING activation in septic mice.[64] Mechanistic study revealed that loss of XBP1 enhances ROS production and induces hepatocellular NLRP3/caspase-1/GSDMD-mediated pyroptosis, which further facilitates mtDNA release.[64] Moreover, XBP1 loss in hepatocytes causes injured mitophagy, which was alleviated by PINK1 overexpression. Restoration of mitophagy alleviates sepsis-associated liver injury through inactivating macrophage STING in XBP1 deficient mice.[64] XBP1-mediated activation of hepatocyte pyroptosis, mitophagy, and STING in macrophages were observed in the livers of human patients with sepsis-associated liver injury.[64] Together, these results suggest that XBP1 knockout promotes hepatic pyroptosis by damaging mitophagy and inducing mtDNA-stimulated cGAS-STING axis activity within

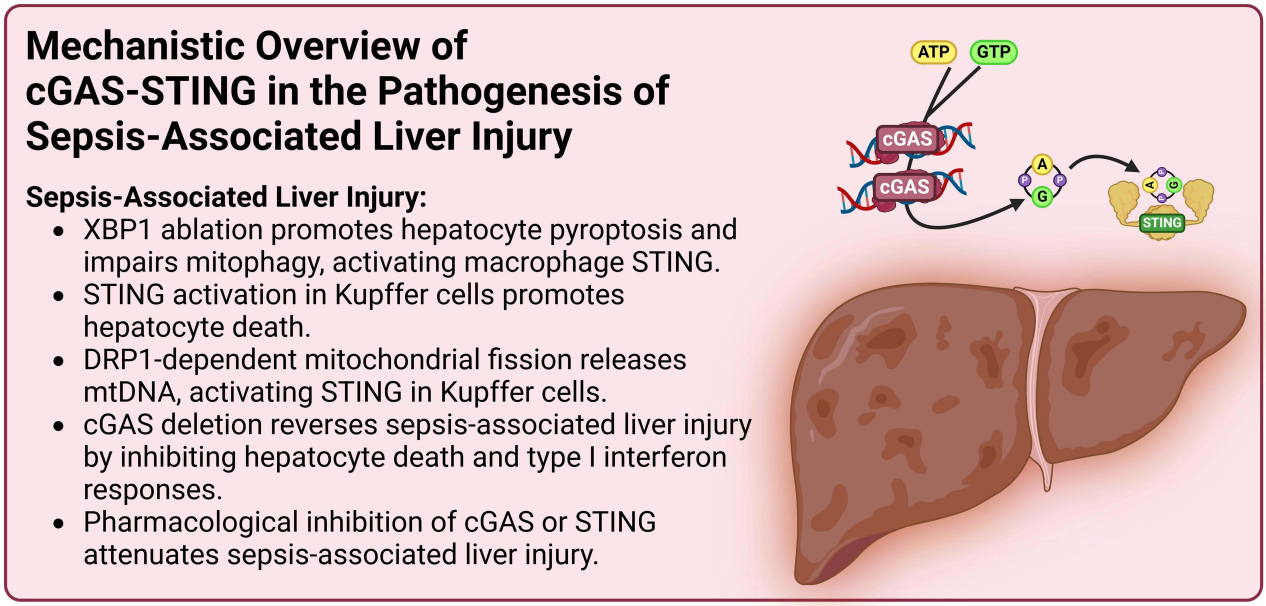

Figure 4 Overview of cGAS-STING contributes to the pathogenesis of sepsis-associated liver injury. cGAS-STING contributes to sepsis-associated liver injury by promoting hepatocyte death, responding to sepsis-induced mtDNA release, and when inhibited attenuates injury.

macrophages.[64] Activated STING in Kupffer cells (KCs) from LPS-induced wild type mice promotes hepatocyte death.[72] Loss of STING suppresses STING agonist DMXAA-mediated enhanced sepsis-associated liver injury. Futher study revealed that STING was activated by dynamin-related protein 1 (DRP1)-dependent mitochondrial fission-mediated mtDNA release in LPS-challenged KCs. LPS DRP1-dependently facilitates production of mitochondrial ROS, which enhances mtDNA release to activate STING in KCs.[72] Mdivi-1 a inhibitor of DRP1, attenuates sepsis-associated liver injury through inhibiting LPS-mediated activation of STING in KCs derived from septic mice. Together, these results indicate that STING senses the DRP1-mediated release of mtDNA in KCs, where STING activation induces sepsis-associated liver injury.[72] Activated cGAS was observed in CLP or LPS plus d-galactosamine (GalN)-induced sepsis mice.[73] Deletion of cGAS reverses liver injury and hepatocyte death in CLP- or LPS/GalN-induced septic mice. STING deletion in hepatocytes also suppresses sepsis-associated liver injury, which can be pharmacologically phenocopied by inhibiting STING by H-151 or cGAS by RU.521.[73] In addition, recombinant interferon-β (rIFNβ) reverses cGAS depletion-mediated protection against sepsis-associated liver injury in LPS and GalN-induced hepatocyte death.[73] Cumulatively, these results suggest that cGAS-STING facilitates sepsis-associated liver injury by both hepatocyte death and type I IFN responses.[73] In summary, these cumulative studies indicate that cGAS-STING is involved in the genesis of sepsis-associated liver injury.

Liver Ischemia-Reperfusion Injury

Enhanced activation of NLRP3 was found in the macrophages and livers of aged mice with post-ischemia-reperfusion. NLRP3 knockout within macrophages prevents liver injury and intrahepatic inflammation. Increased activation of the STING/TBK1 axis was seen in aged macrophages post-IR and mtDNA exposure. STING inhibition prevented overactive NLRP3 activity and the proinflammatory milieu associated with mtDNA-stimulated BMDMs in aged mice. Macrophage-centric STING knockout was found to reverse aging-mediated intrahepatic inflammation and liver IR injury. In summary, aging enhances liver ischemia-reperfusion injury by inducing STING-induced NLRP3 agonism within macrophages.[74] Within liver IRI STING in hepatic macrophages exhibited enhanced caspase-1 mediated GSDMD processing, further driving IL-1b and IL-18 maturation. Cumulatively, this suggests that STING promotes liver IRI by inducing calcium-dependent pyroptosis in macrophages.[75] Increased STING expression within monocyte-derived macrophages drives hepatic inflammation in liver IRI.[53] Loss of macrophage thioredoxin-interacting protein (TXNIP) promotes cylindromatosis (CYLD), which interacted with NOX4 to

enhance Nrf2 and its target gene 2′,5′ oligoadenylate synthetase-like 1 (OASL1) activity, inhibiting of STING-induced TBK1 activity and hepatocyte damage in liver IRI. These results suggest that the TXNIP regulating CYLD-NRF2-OASL1-axis in macrophages is an essential regulator for STING/TBK1-induced immune and cell death pathways in IR stress-induced liver inflammatory injury.[54] Increased mixed-lineage kinase domain-like protein (MLKL) was observed in liver tissues of hepatic IR male C57BL/6 J mice.[76] Loss of MLKL attenuates liver IR injury, cGAS-STING axis activation in intrahepatic macrophages, which has been found to be reversed by STING agonists. Loss of MLKL increases mitophagy mediated by PTEN-induced kinase 1 (PINK1), which suppresses STING activity in macrophages and reduces oxidative DNA damage in hepatocytes.[76] These findings indicate that MLKL ablation promotes PINK1-mediated mitophagy activation to inhibit oxidative DNA damage in hepatocytes, thereby suppressing macrophage cGAS-STING activation and inflammatory liver IR injury.[76] Aging inhibits MerTK (c-mer proto-oncogene tyrosine kinase)-mediated macrophage efferocytosis and promotes macrophage STING signaling and hepatic inflammation in liver IR injury.[55] Decreased protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1G (PPM1G) and increased inflammatory cytokines were observed in a hypoxia/reperfusion (H/R) model in RAW 264.7 cells.[77] Overexpression of PPM1G inhibits cytokine release and decreases STING phosphorylation. Silencing PPM1G enhances STING phosphorylation. Ablation of PPM1G promotes hepatic damage, apoptosis, and transaminases release. Cumulatively, PPM1G attenuates liver IRI through inhibiting activation of STING.[77] Up-regulated PCSK9 is observed in liver IR-induced male C57BL6 and promotes hepatic ischemia-reperfusion injury. Hepatic PCSK9 expression prevents PINK1/Parkin-mediated mitophagy, inducing STING/NRLP3 axis inflammation in hepatic IRI.[78] Decreased SIRT3 protein and enhanced cGAS-STING axis activity are seen in hepatic ischemia-reperfusion injury in mice. Hepatic ischemia-reperfusion induces hepatocytes damages through promoting inflammation via activating the cGAS-STING pathway.[79] Inhibition of SIRT3 aggravates hepatocyte damage through activating cGAS via promoting nuclear translocation of p65 to facilitates cGAS transcription.[79]

Radiation-Induced Liver Disease

Radiation-induced hepatocytes cell death causes massive dsDNA release into the hepatic tissue interstitial fluid (TIF). These dsDNA were engulfed by non-parenchymal cells (NPCs) to activate cGAS-STING, eliciting the expression of IFN-1, which put hepatocytes on oxidative stress and deteriorates radiation-induced liver disease.[66] m^6A-mediated cGAS-STING regulation contribute to radiation-induced liver disease. X-ray irradiation induces AlkB homolog 5 (ALKBH5) to recruit and demethylate m^6A within to the 3′-UTR of HMGB1, leading to stimulate STING-IRF3 signaling. Silencing ALKBH5 inhibits HMGB1 transcription.[65] Loss of ALKBH5 or silencing HMGB1 attenuates IFN-1 synthesis and hepatic apoptosis.[65] Ablation of ALKBH5 abolishes the activation of HMGB1-induced STING activity and suppresses hepatic inflammation, analogous to irradiated $STING^{-/-}$ mice.[65] All together, these results suggest that ALKBH5-mediated activation of HMGB1-STING contributes to radiation-induced liver disease. Irradiation increases m^6A modification levels and the expression of the m^6A writer methyltransferase-like 3 (METTL3) in human KCs. Under the help by the reader IGF2BP2, METTL3 facilitates the methylation of TEAD1 mRNA to promote its mRNA stability and expression of TEAD1, promoting STING-NLRP3 axis activation.[80] Ablation of METTL3/TEAD1 reverses the activation of STING-NLRP3 activity, therefore inhibiting inflammatory cytokines and hepatocyte apoptosis.[80]

Chronic Liver Disease

Iron increases the expression of cGAS, STING, TBK1, IRF-3, and NF-κB in HepG2 cells and murine livers. Ferric ammonium citrate upregulates inflammation within the liver driven by IFN-β in HepG2 cells and mice. Iron overload was found to enhance the pathogenesis of chronic liver disease by stimulating cGAS-STING axis promoted chronic inflammation, identifying a new potential therapeutic target against chronic liver disease, such as alcoholic liver disease and metabolic dysfunction-associated fatty liver disease.[81–83]

Ethanol induces ERS and triggers the association and phosphorylation of IRF3 by STING.[84] IRF3 in association with Bax, resulting in hepatocyte apoptosis. Ablation of STING inhibits ethanol or ER stress-induced IRF3 phosphorylation, while IRF3 knockout prevents hepatocyte apoptosis. IRF3-mediated pathogenesis of alcoholic liver disease (ALD) was not dependent on inflammation or IFN-1 activity, indicating that STING/IRF3 are key determinants of ALD, linking ERS with hepatocyte apoptosis.[84] Upregulated STING was found in Gao binge ethanol model mice. In hepatic KCs STING functions as a mtDNA sensor to aggravate hepatocyte apoptosis in the Gao binge ethanol model.[85] Decreased hepatic

dynamin-related protein 1 (DRP1) and accumulated hepatic megamitochondria were observed in human alcoholic hepatitis and alcohol-fed mice.[86] Ablation of DRP1 increases hepatic exposure to mtDNA and mitochondrial dysfunction, promoting cGAS/STING-IFN-1 activity and liver injury in alcohol-fed mice.[86]

Metabolic dysfunction-associated fatty liver disease (MAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD) has become one of the most common chronic liver diseases worldwide, approximately 30% of adults and 70%~80% of patients with obesity and diabetes suffer from MAFLD.[82] Upregulated STING and IRF3 were observed in livers of HFD-induced obese mouse and in free fatty acid (FFA)-induced L-O2 cells[87](Figure 5). Silencing STING or IRF3 reduces FFA-promoted hepatic apoptosis and inflammation. Knockout of STING/IRF3 induces glycogen storage and alleviates lipid accumulation by enhancing the expression of pro-glycolytic and pro-lipid catabolic while repressing the expression of gluconeogenic and lipid synthetic enzymes.[87] Together, the data suggests that STING-IRF3 axis activity induces hepatocyte inflammation, apoptosis and induces metabolic disorders in NAFLD, highlighting a novel therapeutic vector for treatment against NAFLD development and progression.[87] During obesity and NAFLD, saturated fatty acid (SFA) activates cGAS-STING and ensued TBK1 to enhance the synthesis of p62-ubiquitin aggregates, resulting in defected autophagy. During NASH, damaged autophagy cannot remove the intra-hepatocyte p62-ubiquitin aggregates, creating large protein-inclusions which promote ROS accumulation and the development of fibrosis. Lipotoxicity increases TBK1 activity in hepatic stellate cells and leukocytes, further promoting fibrotic pathology.[88]

STING is causally associated with the pathogenesis of NAFLD. Increased STING was seen in both the livers of human NAFLD patients or HFD-steatotic mice.[89] STING knockout in mice and mice myeloid cells reduced steatosis, fibrosis, and inflammation in HFD or methionine/choline-deficient diet (MCD) mice. Macrophages from STING knockout mice decreases reduces the extent of inflammatory responses post-LPS/cGAMP exposure. STING knockout macrophages co-cultured with hepatocytes and stellate cells in the presence of DMXAA had lower steatosis and inflammation compared to those with control macrophages. Macrophage STING knockout reduces the severity of liver fibrosis and inflammation in mice.[89] In aggregate, these results suggest that STING activation in macrophages promotes the paracrine secretion of cytokines, which promote hepatic inflammation, steatosis, and fibrosis.[89] This observation was corroborated by other study, which found that STING expression in macrophages was correlated with the extent of liver inflammation and fibrosis in NAFLD patients.[90] Ablation of STING alleviates steatosis, inflammation, and fibrosis in livers in HFD and MCD diet murine models of NASH.[91] Knockout of STING enhances fasting glucose levels in mice orthogonal to insulin-levels, but improves HFD-induced weight gain, insulin resistance, reduces levels of triglycerides, cholesterol, and LDL in serum, while increasing HDL. Hepatocyte mtDNA within HFD-fed mice promotes IL-6 and TNF-α expression in cultured KCs, which was inhibited by STING ablation or BAY11-7082. Activation of STING promotes inflammation and hepatic steatosis in wide type mice, but not in STING knockout mice. In summary, these results suggest that STING-elicited inflammation in KCs drives progression into NASH.[91] This observation was corroborated by other study, which reported loss of STING attenuates NAFLD.[92]

Sterol regulatory element binding protein cleavage-activating protein (SCAP), a cholesterol sensor in macrophage contributes to NAFLD metaflammation by agonizing the STING-NF-κB pathway.[93] Increased SCAP in macrophage was

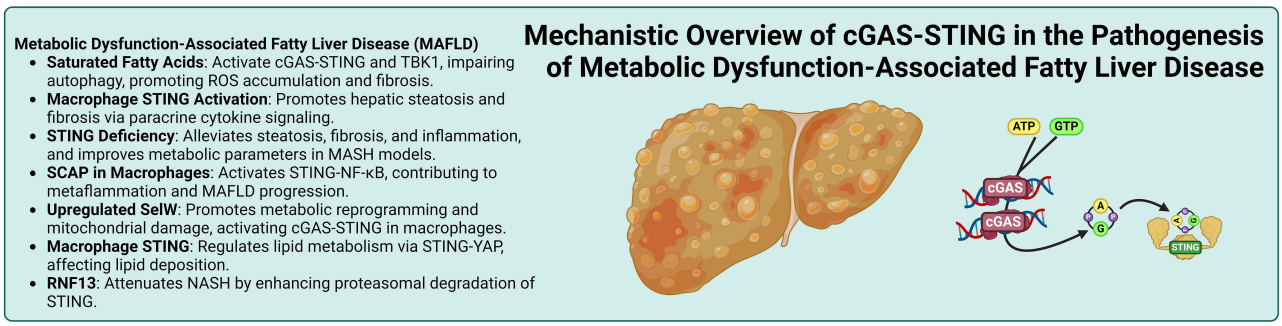

Figure 5 Mechanistic overview of cGAS-STING in the pathogenesis of metabolic dysfunction-associated fatty liver disease. cGAS-STING is pathogenic to MAFLD, in which it contributes to hepatic inflammation, ROS accumulation, impaired autophagy, steatosis, and fibrosis.

observed in the liver and adipose tissues of Paigen diet (PD) mice. Ablation of macrophage SCAP attenuates PD-promoted ectopic lipid deposition and metaflammation and by reducing hepatic STING-NF-κB axis activity.[93] Upregulated selenoprotein W (SelW) expression was observed in the livers of NAFLD patients.[94] SelW promotes pyruvate kinase M2 (PKM2)-mediated metabolic reprogramming to transactivate HIF-1α, which mediates mitochondrial apoptosis, promoting mitochondrial damage, excessive ROS release, and mtDNA secretion.[94] SelW injures mitochondria, leading to mito-ROS production to activate pyroptosis and mtDNA leakage, which activates the macrophage cGAS-STING axis, promoting the M1 phenotype.[94] Cumulatively, these results suggest that SelW induces hepatocyte pyroptosis and apoptosis by activating the macrophage cGAS/STING axis, enhancing NAFLD progression.[94]

Loss of STING in macrophages enhances nuclear YAP activity, suppresses steatosis, and reduces lipid droplet protein perilipin 2 expression in response to high-fat diet (HFD)-induced oxidative stress.[95] Disruption of STING and YAP augments perilipin 2 and HFD-induced lipid deposition. The YAP target gene TMEM205 is critical for activating AMPKα, which combines with mitofusin 2 and induces the PDI-HIF-1α axis, enhancing chaperone-driven autophagic degradation of perilipin 2. Therefore, it is clear that the macrophage STING-YAP axis exerts a pathogenic effect on lipid metabolism, driving NAFLD.[95]

Gut microbial DNA-containing extracellular vesicles (mEVs) translocation can insert microbial DNA into hepatocytes and HSCs, enhancing hepatic inflammation and fibrosis through the cGAS/STING axis.[96]

PTM regulates STING in NAFLD. Upregulated RING finger protein 13 (RNF13) protein is observed in the livers of NASH patients. Hepatic knockout of RNF13 exacerbates steatosis, insulin resistance, inflammation, fibrosis, and cell, which can be reversed by RNF13 overexpression. RNF13 enhances the ubiquitin/proteasome-driven degradation of STING. These results suggest that RNF13 attenuates NASH through enhancing proteasomal degradation of STING.[97]

Liver Fibrosis

cGAS/STING axis activity is crucial in liver fibrosis, specifically by promoting sinusoidal microthromboses, which enhances portal vein pressure in CCl_4-induced mice[98](Figure 6). XBP1-inducted STING activation in macrophages additionally enhances liver fibrosis.[99] CCl_4 injection, MCD diet, or bile duct ligation promotes macrophages mtDNA cytosolic leakage to activate STING. XBP1 directly inhibits the transcription of BCL2/adenovirus E1B interacting protein 3 (BNIP3) in macrophages.[99] XBP1 knockout inhibits the cGAS/STING/NLRP3 axis by enhancing macrophage BNIP3-mediated mitophagy. STING, XBP1, or NLRP3 knockout in myeloid is anti-fibrotic in mice.[99] Together, these results suggest XBP1 promotes liver fibrosis through activating cGAS/STING/NLRP3 via inhibiting BNIP3. Ablation of Parkin aggravates CCl_4-induced cell death induction, autophagic suppression, and liver fibrosis.[100] Parkin prevents mtDNA/STING signaling induced by CCl_4 or knockout of *ENDOG*. Voltage-dependent anion channels 1 (VDAC1) ubiquitination by Parkin inhibits liver fibrosis by preventing VDAC1 oligomerization and mtDNA release, preventing STING activation within HSCs. In summary, these data unveil a novel Parkin/mtDNA axis mediated by VDAC1 oligomerization, driving STING activation and liver fibrosis.[100]

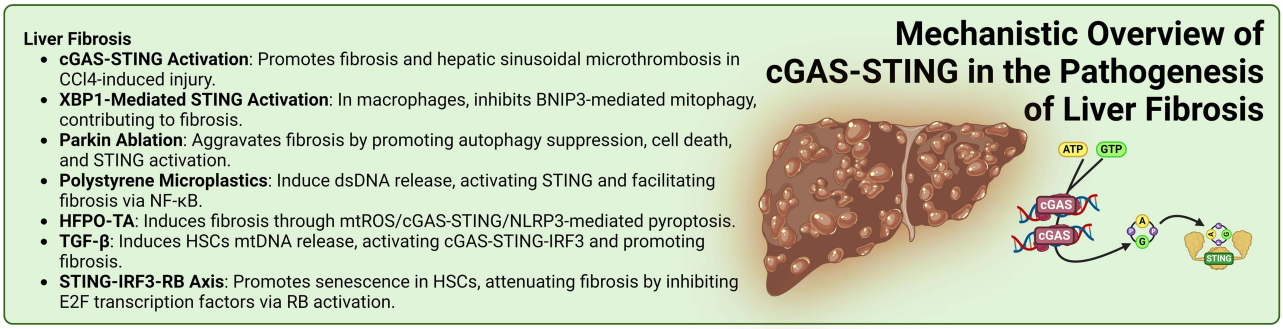

Figure 6 Mechanistic overview of cGAS-STING in the pathogenesis of liver fibrosis. cGAS-STING is pathogenic in liver fibrosis, being activated by XBP1 and TGF-b, inducing NLRP3-induced pyroptosis and promoting HSC senescence.

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Polystyrene microplastics induce dsDNA release to cytoplasm to activate STING, which initiates NF-κB activation mediated inflammation and fibrosis.[101] Hexafluoropropylene oxide trimer acid (HFPO-TA) induces liver damage via mtROS/cGAS-STING/NLRP3 axis -induced pyroptosis in mice.[102] TGF-β induces HSCs mtDNA release through voltage-dependent anion channels (VDACs), which allows for mtDNA-caps on the external mitochondrial membrane, recruiting cGAS and activating the cGAS/STING/IRF3 axis. STING inhibitors therefore reduce liver fibrosis.[103]

Recent study has shown that STING induces hepatic fibrosis by epigenetically stimulating NLRP3-driven inflammation and pyroptosis in hepatocytes.[104] The STING/NLRP3 axis is agonized in mice given olive oil or CCl_4. STING knockout prevents hepatic inflammation, pyroptosis, and fibrosis. STING promotes hepatic pyroptosis by agonizing the NLRP3 inflammasome.[104] H3K4-specific histone methyltransferase WD repeat-containing protein 5 (WDR5)/DOT1-like histone H3K79 methyltransferase (DOT1L)-mediated histone methylation facilitates IRF3 transcription at the NLRP3 promoter, mediating STING-driven NLRP3 expression.[104] Cumulatively, the results share that epigenetic mechanisms promote liver fibrosis through the STING-WDR5/DOT1L/IRF3-NLRP3 axis.[104]

STING-IRF3-retinoblastoma (RB) axis was found to mitigate hepatic fibrosis by promoting HSC senescence.[105] Hydroxyurea (HU) is a well-defined inducer of cGAS-STING signaling and cellular senescence, promoting the activation of IRF3. In the nucleus, IRF3 interacts with the key cell cycle regulator RB. This complex prevents CDK4/6-cyclin-RB from activating RB, which then inhibits E2F transcription factors, promoting senescence in activated HSCs and attenuating liver fibrosis.[105]

Autoimmune Hepatitis

Concanavalin A (ConA) induced liver injury during autoimmune hepatitis. Manganese promotes hepatic injury by stimulating the cGAS-STING axis and its inflammatory response in ConA-induced mice.[67] Macrophage STING triggers iron dysregulation, thereby leading to necrotic damage in ConA-induced mice. Ablation of KCs STING reduces liver injury by suppressing macrophage infiltration and iron accumulation via suppressing the TF/TfR axis in ConA-induced hepatic injury, suggesting STING maybe trigger ConA-induced liver injury through inducing ferroptosis.[106] Indeed, ferroptosis inhibitors ferrostatin-1 and DFO alleviates ConA-induced liver damage.[106]

Therapeutic Potential of cGAS-STING Inhibition in Liver Diseases Therapy

Several compounds have already demonstrated therapeutic potential by targeting cGAS-STING in liver diseases (Figure 7). A summary of compounds functions as cGAS-STING inhibitors are itemized in Table 1 and Figure 8.

Acute Liver Injury

Ginsenoside Rd protects mice from CCl_4-induced acute liver injury by inhibiting ferroptosis via the suppression of cGAS/STING pathway.[107] Pterostilbene (PTE)-loaded Soluplus/poloxamer 188 mixed micelles (PTE-MMs) inhibits H_2O_2-induced HepG2 cell proliferation, loss of mitochondrial membrane potential.[58] It inhibits H_2O_2-induced DNA damage and activation of cGAS-STING. PTE-MMs inhibits acetaminophen-induced liver injury and decreases in serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). PTE-MMs also inhibits acetaminophen (APAP)-induced DNA damage and activation of cGAS-STING in liver tissues.[58] The combination of recombinant IL-33 and RU.521 improves survival and decreases the APAP-mediated increases of serum levels of ALT/AST. Jujuboside B (JuB) inhibits APAP-induced oxidative stress and the pro-inflammatory cytokines and hepatocyte apoptosis, maybe resulting from upreguleting Nrf2/HO-1/NQO-1 pathway and inhibiting STING pathway activation in C57BL/6 J mice.[59] A potent and selective NLRP3 inhibitor, MCC950 attenuates APAP-triggered liver injury and inflammation.[69] The polyvinyl pyrrolidone (PVP K17) and poloxamer 188, and encapsulated Hesperidin (Hes) (Hes-MMs) reduces liver injury through inhibiting the mtDNA-cGAS-STING signaling pathway in liver IRI.[63] Selectively inhibiting STING by C-176 inhibits activation of STING and decreases inflammatory cytokines in a hypoxia/reperfusion (H/R)-induced RAW 264.7. C-176 inhibits PPM1G inhibition-induced liver damage and transaminase release.[77] LDK378 decreases the production of IFN-β, TNF-α, and IL-6, downregulates STING protein and mRNA levels and ensued decreased expression of phosphorylated IRF3, TBK1, IκB, and p65.[124] Inhibiting ALK-STING pathway confers protection against sepsis-induced acute liver injury.[124] Compound 30, a fusidic acid derivatives works as a novel STING inhibitors to alleviate sepsis-induced acute liver

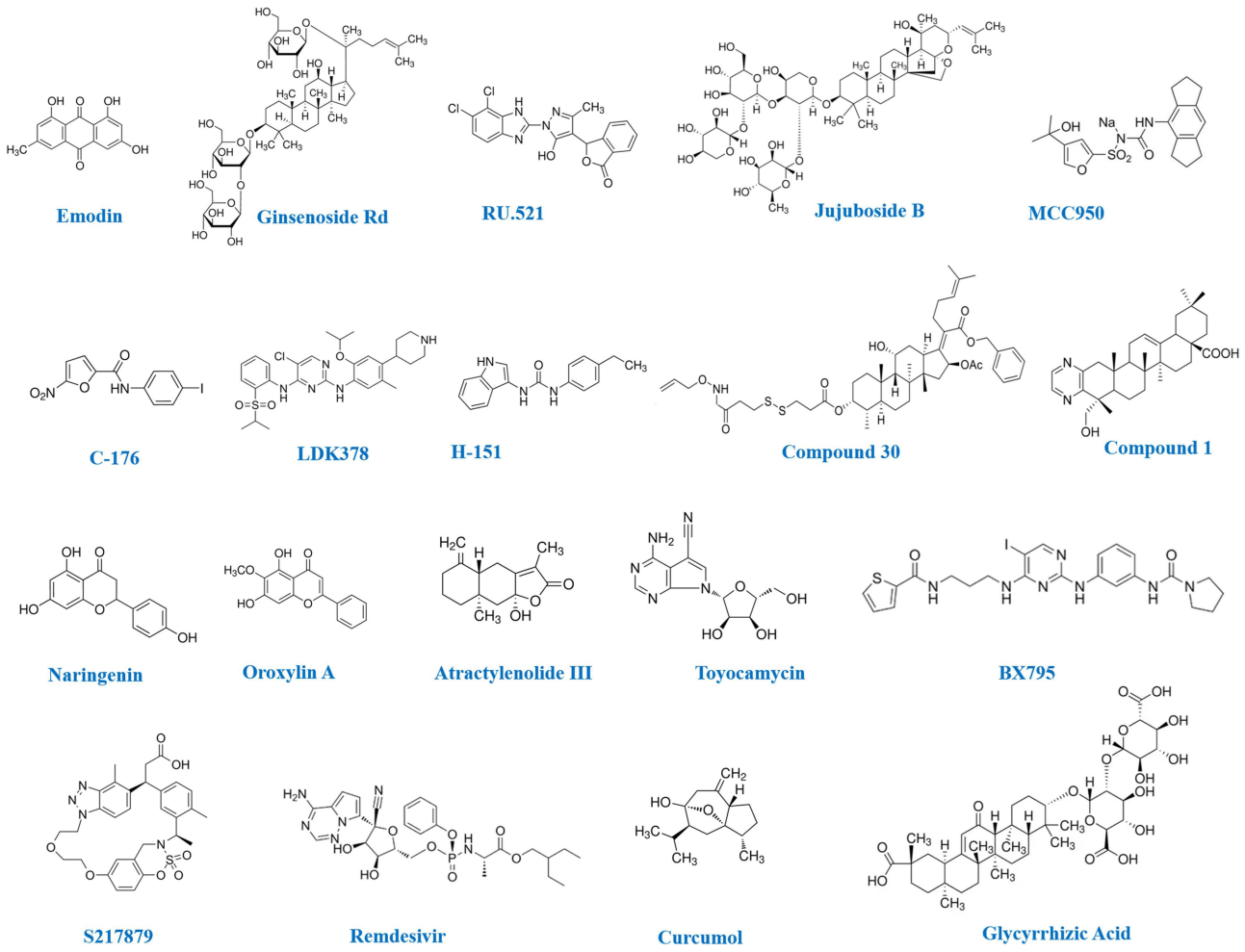

Figure 7 Chemical structures of small molecules targeting cGAS-STING signaling pathway to treat liver diseases.

injury, evidenced by inhibiting activation of IRF3, TBK1, and NF-κB signaling pathways via suppressing STING.[109] Loss of STING in hepatocyte alleviates sepsis-induced acute liver injury, which can be phenocopied by pharmacological inhibition of STING or cGAS.[73] Compound 1 is the hederagenin derivatives and alleviates sepsis-induced acute liver injury through suppressing STING-NF-κB signaling.[110] A selective STING inhibitor C-176 attenuates sepsis-induced acute liver injury through suppressing STING, evidenced by decreased levels of STING and phosphorylated TBK, p65, IRF3, and IκB-α in the liver and decreased mRNA levels of TNF-α, IL-6, and IFN-β.[109]

Fibrosis

TBK1 inhibition by BX795 prevents formation of ubiquitin-p62 aggregates in cultured hepatocytes and obesity and NASH mouse.[88] BX795 suppresses p62 phosphorylation and protein inclusion in livers of obese mice. BX795 suppresses NASH-induced liver fibrosis.[88] Inhibition of STING by C-176 alleviates microplastics-induced liver fibrosis through blocking the NF-κB translocation and fibronectin expression.[101] Pharmacologically inhibiting XBP1 by toyocamycin alleviates liver fibrosis in mice challenged by bile duct ligation, carbon tetrachloride injection, or a methionine/choline-deficient diet.[99] Naringenin inhibits hepatic stellate cell (HSC) activation and inflammation through inactivating cGAS-STING, thus preventing liver injury and liver fibrosis in CCl4-induced mice.[113] Oroxylin A attenuates liver fibrosis through promoting HSC senescence by activating the cGAS-STING pathway in bleomycin-induced male C57BL/6 J mice.[115] It also inhibits liver fibrosis through inducing HSC senescence and activating HSC ferritinophagy via activation of cGAS-STING.[114]

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Table 1 Emerging Compounds Targeting cGAS-STING to Attenuate Liver Disease

Diseases	Compounds	Experimental Model	Findings	Ref
ALI	Emodin	C57BL/6 J mice /Acetaminophen	↓ Levels of AST, ALT, and ALP; ↑ALB levels;↓ hepatocellular damage;↓ apoptosis;↓ exhaustion of GSH and SOD;↓MDA; ↑antioxidative enzymes;↓pro-inflammatory factors;↓NLRP3;↓IFN-α, cGAS-STING expression.	[57]
ALI	Ginsenoside Rd	C57BL/6 mice /CCl_4	↓ALI;↓iron, 4-HNE, and 8-hydroxy-2 deoxyguanosine (serum and liver);↑GSH and GPX4 levels;↓ cGAS and STING; erastin reverses the hepatoprotective effect of ginsenoside Rd.	[107]
ALI	RU.521 and recombinant IL-33	C57BL/6N mice / Acetaminophen	↑Survival;↓ liver injury;↓ ALT/AST levels; ↑GSH levels;↓ mRNA level of IFN-β1.	[60]
ALI	PTE-MMs	Kun-Ming KM mice/ Acetaminophen	↓ Injury in liver histopathology;↓ serum AST and ALT; ↑activities of SOD and GSH in liver tissue;↓ DNA damage;↓ cGAS-STING activation.	[58]
ALI	Jujuboside B	C57BL/6 J mice/ Acetaminophen	↓CYP2E1 accumulations;↓acute liver injury;↓ oxidative stress, pro-inflammatory cytokines and hepatocyte apoptosis; ↑Nrf2, HO-1 and NQO-1;↓STING activation.	[59]
ALI	MCC950	C57BL/6J mice/ Acetaminophen	↓Liver injury and inflammation.	[69]
ALI	Hes-MMs	C57BL/6 mice/I/R	↓mtDNA release;↓cGAS-STING;↓liver injury.	[63]
Liver IRI	C-176	C57BL/6 mice/I/R	↓PPM1G inhibition-induced liver damage;↓transaminase release.	[77]
ALI	LDK378	CLP/B6 mice	↓ALT.	[108]
ALI	LDK378	LPS/C57BL/6J mice	↓Endotoxemic lethality;↓organ dysfunction;↓tissue injury;↓proinflammatory cytokine expression and release.	[108]
ALI	RU.521	LPS+D-gal /C57BL/6J mice	↓Death rate;↓liver injury;↓liver dysfunction;decreases plasma and hepatic IFNβ;↓ OAS2, ISG15,IFIT1 and SLFN4 expression of the liver.	[73]
ALI	H-151	LPS+D-gal /C57BL/6J mice	↓Death rate;↓liver injury, liver dysfunction;↓plasma and hepatic IFNβ;↓OAS2, ISG15, IFIT1 and SLFN4 expression of the liver.	[73]
ALI	Compound 30	LPS/BALB/c mice	↓TNF-α, IL-6 and IFN-β;↓phosphorylated TBK1, P65, IRF3, and IκB;↓STING protein and mRNA levels.	[109]
ALI	Compound 1	LPS/BALB/c mice	↓Hemorrhage severity;↓ALT, AST, and ALP;↓mRNA levels of IFN-β, TNF-α, and IL-6;↓STING and phosphorylated TBK, IRF3, p65, and IκB-α in the liver.	[110]
ALI	C-176	LPS/BALB/c mice	↓Hemorrhage severity;↓ALT, AST, and ALP; ↓mRNA levels of TNF-α, IL-6, and IFN-β;↓STING and phosphorylation of TBK, p65, IRF3,and IκB-α in the liver.	[110]
ALI	Mdivi-1	LPS/C57/BL mice	↓Liver injury;↓systemic inflammatory response;↓dynamin-related protein 1;↓activation of STING signaling in Kupffer cells	[72]
ALI	Peptide ST5	CLP/C57BL/6	↓Production of NETs;↓MPO-DNA levels in the supernatant of platelets/neutrophils;↓septic thrombosis;↓ TAT complex; ↑fibrinogen.	[111]
ALI	Total glucosides of paeony	LPS/C57/BL mice	↓Pathological changes;↓ inflammatory and bleeding reactions;↓ALT and AST;↓apoptosis;↓IFN-β;↓TNF-α and IL- 6;↓IFN-β, CXCL10, ISG15, TNF-α and IL-6 mRNA.	[112]
Fibrosis	Naringenin	Male C57BL/6J mice/CCl_4	↓Liver injury;↓liver fibrosis;↓collagen deposition;↓cGAS;↓inflammation.	[113]
Fibrosis	Oroxylin A	Male ICR mice / CCl4	↓Pathological changes;↓collagen deposition;↓liver fibrosis; ↑HSC senescence;↑HSC ferritinophagy; cGAS-STING mediates the Oroxylin A-induced activation of HSC ferritinophagy;↑secretion of cytokines like IFN-β by the cGAS-STING pathway to regulate ferritinophagy; silencing cGAS decreases NCOA4, and a decrease in the content of ROS and iron ions in HSCs.	[114]
Fibrosis	Oroxylin A	Male C57BL/6 J mice/ bleomycin	↑Senescence in HSC by activating the cGAS-STING pathway;↑senescence of HSC, and DNMT3A overexpression partly offset this effect.	[115]
Fibrosis	Atractylenolide III	Human HSC LX-2/ etoposide	↑Senescence of LX2 cells;↓IL-1α, IL-1β, IL6 and IL-8;↓cGAS/NF-κB signaling.	[116]

Fibrosis	C176	Male C57 mice or HL7702 cells/ micro-PS	↓Activation of STING and NF-κB;↓liver damage and fibrosis.	[101]
Fibrosis	Toyocamycin	C57BL/6 mice/CCl4-, BDL-, or MCD	↓Liver fibrosis.	[99]
Radiation-induced liver diseases	H151	Male C57BL/6J mice/8-Gy	↑Survival probability of mice;↓irradiation-induced liver injury;↓hepatic cell damage;↓IL-1β and 1L-18 in liver tissue;↓serum ALT/AST levels.	[80]
Radiation-induced liver diseases	Extracts of Washingtonia robusta	Female rats/γ-irradiated (7.5 Gy)	↓Liver index, ALT, albumin, cholesterol, and ROS levels;↓ increase in STING expression.	[117]
MAFLD	BX796	Hepatocytes and in mouse models of obesity and NASH	↑Formation of ubiquitin-p62 aggregates.	[88]
MAFLD	S217879	Patient-derived precision cut liver slices	↓DNA damage, apoptosis, and inflammation; ↑ antisteatotic effects by improving lipid metabolism; ↑antioxidative stress response; ↓fibrogenesis by preventing HSCs activation.	[118]
MAFLD	Lingguizhugan decoction	Male C57BL/6J mice / HFD	↓Hepatic steatosis; ↓hepatic mitochondrial damage; ↓oxidative stress; ↓mitochondrial DNA release;↓ STING;↓infiltration of STING-positive macrophages;↓DMXAA or LPS-mediated activation of STING-TBK1-NF-κB pathway in liver macrophage;↓release of IFNβ and TNFα.	[119]
MAFLD	Licorice extract	C57BL/6 mice /MCD diet	↓cGAS-STING activation;↓oligomerization of STING;↓inflammation and fibrosis.	[120]
MAFLD	C-176	C57BL/6 mice/MCD diet	↓Pathology and fibrosis.	[120]
MAFLD	Remdesivir	C57BL/6 mice/HFD	↓Lipid deposition;↓systematic and hepatic inflammation;↓cGAS-STING and its down-streaming factor IRF.	[121]
AFLD	Curcumol	Male C57BL/6J mice / ethanol liquid diet	↓Cellular senescence;↓dysfunction of the telomere and telomerase system;↓SA-β-gal activity and p16 and p21;↓formation of CCF;↓cGAS-STING activation;↓SASP-related inflammatory factors' secretion;↑ nuclear membrane integrity; ↓interaction of LC3B with lamin B1.	[122]
AFLD	Glycyrrhizic Acid		↓Area of oil red staining in liver;↓pyroptotic bodies;↓NOX2, NOX3, STING, p-SYK, NLRP3, p-PDE4B, IL-1β, Caspase-1, GSDMD, and Caspase-4; ↑protein expression of p-SHP1 and Nrf2.	[123]

Abbreviations: 4-HNE, 4-hydroxynonenal; AFLD, alcoholic fatty liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Bindarit, CCL2 inhibitor; CCF, cytoplasmic chromatin fragments; ISG15, interferon-stimulated gene 15; ZnONPs, Zinc oxide nanoparticles; Amlexanox, TBK1 inhibitor; PPD, 20(S)-Protopanaxadiol; GSH, glutathione; GPX4, glutathione peroxidase 4; PTE-MMs, Pterostilbene-loaded Soluplus/poloxamer 188 mixed micelles (PTE-MMs); HSC, hepatic stellate cell; MAFLD, metabolic dysfunction-associated fatty liver disease; MCD, methionine-choline-deficient; SA-β-gal, senescence-associated β-galactosidase; SASP, senescence-associated secretory phenotype; OGD/R, oxygen-glucose deprivation/reperfusion; NF-κB, nuclear factor-κB; ICAM-1, intercellular adhesion molecule 1; IFN-β, interferon-β; IRF-3, interferon regulatory protein-3; IRF-7, Interferon regulatory factor 7; TBK1, tank-binding kinase 1; TNF-α, tumor necrosis factor-alpha; Toyocamycin, a selective XBP1 inhibitor.

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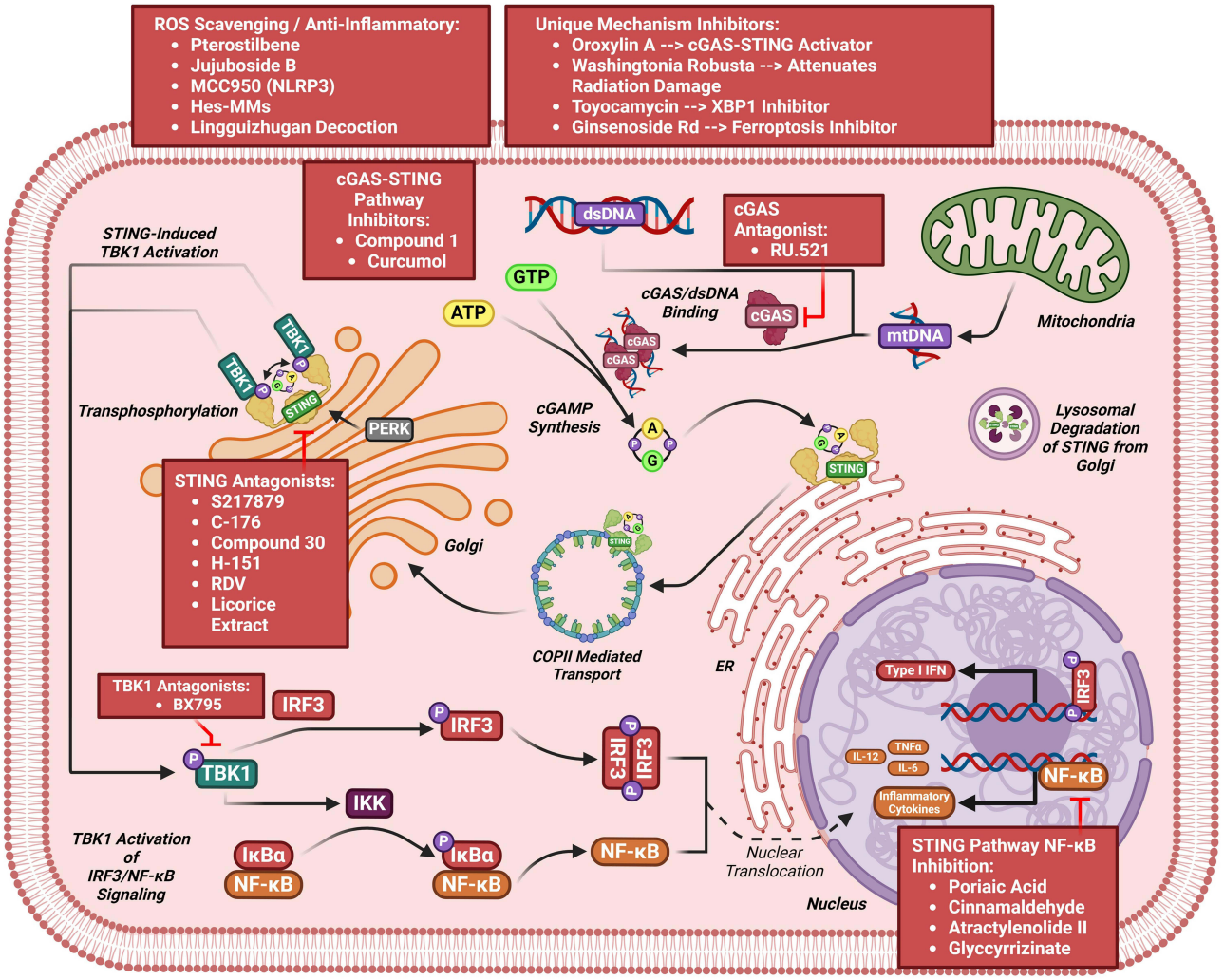

Figure 8 Antagonists of cGAS-STING pathway for liver diseases therapy. Multiple classes of cGAS-STING antagonists have shown protective effect in liver diseases.

Radiation-Induced Liver Disease

Extracts of Washingtonia robusta decreases liver index, albumin, ALT, cholesterol, and ROS levels and decreases expression of STING.[117] STING inhibition by H151 enhances survival probability of mice and attenuates irradiation-induced hepatic cell damage through decreasing STING-NLRP3-induced secretion of cytokine 1L-18 and IL-1βin liver tissue.[80]

MAFLD

A new NRF2 activator S217879 prevents DNA damage, apoptosis, and STING-mediated inflammation. S217879 exerts antisteatotic effects by improving lipid metabolism. It induces a potent antioxidative stress response through activating Nrf2. It inhibits fibrogenesis by preventing HSCs activation in human patient-derived precision cut liver slices (PCLS) in patients with MAFLD.[118] Remdesivir reduces lipid deposition, suppresses the systematic and hepatic inflammation, restrains cGAS-STING and its down-streaming factor IRF.[121] A traditional Chinese herbal decoction, Lingguizhugan decoction (LGZG) attenuates hepatic steatosis, oxidative stress, hepatic mitochondrial damage, mitochondrial DNA release-induced activation of STING and STING-positive macrophages infiltration in the livers of HFD fed mice.[119] Poriaic acid, cinnamaldehyde, glycyrrhizinate, and atractylenolide II, the critical components of LGZG directly inhibits DMXAA and LPS-induced STING-TBK1-NF-κB activation in liver macrophages, thereby decreasing the release of IFNβ and TNFα. LGZG alleviates HFD-induced hepatic-lipid deposition by suppressing liver macrophages STING-

TBK1-NF-κB axis.[119] Licorice extract protects against NASH by inhibiting the cGAS-STING pathway. Licorice extract reduces inflammation and fibrosis through attenuating cGAS-STING pathway activation via inhibiting the oligomerization of STING in MCD diet-induced NASH mice models.[120]

Alcoholic Fatty Liver Disease

Curcumol alleviates ethanol-induced cellular senescence, as evidenced by a decreased senescence-related markers p16 and p21, decreased activity of senescence-associated β-galactosidase (SA-β-gal), and dysfunction of the telomere and telomerase system.[122] Curcumol inhibits ethanol-induced formation of cytoplasmic chromatin fragments by decreasing interaction of LC3B with lamin B1 and maintaining integrity of nuclear membrane, thereby activating cGAS-STING to reduce senescence-associated secretory phenotype (SASP)-related inflammatory factors' secretion. Together, these results suggest that curcumol ameliorates AFLD through inhibition of hepatocyte senescence resulting from blocking interaction of LC3B and lamin B1 and inactivating cGAS-STING pathway.[122] Glycyrrhizic acid ameliorates genesis of alcoholic fatty liver by regulating the SHP1/SYK and STING in macrophages, thereby suppressing hepatic lipid peroxidation and pyroptosis.[123]

Conclusions and Perspectives

Accumulating evidence over the past five years has established the pivotal role of cGAS-STING pathway activation in hepatic pathophysiology. Recent advances demonstrate that pharmacological modulation of this pathway represents an emerging therapeutic paradigm for hepatic disorders. Notably, numerous natural compounds exhibit disease-modifying effects through bidirectional regulation of cGAS-STING signaling. This review systematically examines: (1) Core activation mechanisms of cGAS-STING signaling; (2) Mechanistic links between pathway dysregulation and hepatic pathogenesis; (3) Bioactive compounds demonstrating therapeutic potential through pathway modulation. Our analysis highlights cGAS-STING antagonists as promising candidates for targeted hepatotherapy.

However, many questions remain to be answered. First, the precise spatiotemporal activation dynamics of cGAS-STING signaling in hepatic microenvironments remain elusive. Single-cell spatial transcriptomics could delineate cell-type specific activation patterns. Second, while mitochondrial dysfunction and nuclear DNA leakage are established triggers, their downstream transduction cascades in hepatocytes require mechanistic clarification. Third, the regulatory landscape encompassing post-translational modifications (eg, phosphorylation, ubiquitination) and epigenetic control of cGAS-STING in chronic liver diseases warrants systematic investigation. Fourth, pathway interactions with regulated cell death modalities-particularly the ferroptosis-pyroptosis axis in steatohepatitis-demand disease-specific characterization. Fifth, translational challenges persist: current findings derive predominantly from rodent models, necessitating human biomarker studies and organoid-based validation.

Notwithstanding these challenges, therapeutic targeting of cGAS-STING signaling emerges as a transformative approach in hepatology. While deeper mechanistic understanding is imperative, first-generation inhibitors already show promise in preclinical models. Future research should bridge molecular insights with clinical translation, particularly through combinatorial regimens integrating pathway modulators with existing therapies.

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Disclosure

The authors declare no competing interests in this work.

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