Biology Direct

REVIEW Open Access

cGAS-STING targeting offers therapy choice in lung diseases

Yu Wang[1†], Xuan Zhang[2†], Weixue Wang[1], Yi Zhang[1], Joshua S. Fleishman[3*] and Hongquan Wang[1*]

Abstract
Cyclic GMP/AMP (cGAMP) synthase (cGAS), along with the endoplasmic reticulum (ER)-associated stimulator of interferon genes (STING), are crucial elements of the type 1 interferon response. cGAS senses microbial DNA and self-DNA, labeling cGAS-STING as a crucial mechanism in autoimmunity, sterile inflammatory responses, and cellular senescence. However, chronic and aberrant activation of the cGAS-STING axis results in inflammatory and autoimmune diseases. cGAS-STING has emerged as a vital mechanism driving inflammation-related diseases, including lung diseases. Insights into the biology of the cGAS-STING pathway have enabled the discovery of small-molecule agents which have the potential to inhibit the cGAS-STING axis in lung diseases. In this review, we first outline the principal components of the cGAS-STING signaling cascade. Then, we discuss recent research that highlights general mechanisms by which cGAS-STING contributes to lung diseases. Then, we focus on summarizing a list of bioactive small-molecule compounds which inhibit the cGAS-STING pathway, reviewing their potential mechanisms.These review highlights a novel groundbreaking therapeutic possibilities through targeting cGAS-STING in lung diseases.

Keywords cGAS, STING, Antagonist, Lung diseases

Introduction

Cyclic GMP/AMP (cGAMP) synthase (cGAS), along with the endoplasmic reticulum (ER)-associated stimulator of interferon genes (STING), are crucial elements of the innate immune response [1, 2]. Microbial DNA is a pathogen-associated molecular pattern (PAMP), the main "molecular threat" needed to activate the DNA sensing protein cGAS. cGAS promotes the synthesis of the cyclic dinucleotide cGAMP which binds to STING, initiating trafficking and migration from the ER to the Golgi, where it recruits TANK-binding kinase 1 (TBK1) and the transcription factor interferon regulatory factor 3 (IRF3). Phosphorylated IRF3 dimerizes and translocates into the nucleus, enhancing the expression of type I interferons (IFN-I) and IFN-stimulated genes (ISGs) [2–4]. Increasing evidence reveals that the over-activation and aberrant regulation of the cGAS-STING axis triggers undesired outcomes such as neuroinflammation

†Yu Wang and Xuan Zhang contributed equally to this work.

*Correspondence:
Joshua S. Fleishman
joshua.fleishman18@my.stjohns.edu
Hongquan Wang
whongquan@alu.fudan.edu.cn
[1]Department of Geriatrics, Aerospace Center Hospital, Peking University Aerospace School of Clinical Medicine, Beijing 100049, China
[2]Clinical Pharmacology Research Center, Peking Union Medical College Hospital, State Key Laboratory of Complex Severe and Rare Diseases, NMPA Key Laboratory for Clinical Research and Evaluation of Drug, Beijing Key Laboratory of Clinical PK & PD Investigation for Innovative Drugs, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China
[3]Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, Queens, NY 11439, USA

and neurodegeneration, contributing to neurological disorders and accelerating disease progression [1–3, 5–8]. In the past decade, interest has increased in elucidating the role of cGAS-STING in lung diseases. Given the essential role of cGAS-STING signaling in the pathogenesis of these diseases, drug discovery targeting the cGAS-STING axis has expanded rapidly [9, 10]. cGAS-STING pathway modulators are new and attractive targets for targeted medicine against these diseases.

In this review, we first outline the principal components of the cGAS-STING signaling cascade. From such we discuss recent research that highlights general mechanisms by which cGAS-STING contributes to lung diseases. Then, we summarize a list of bioactive small-molecule compounds which modulate the cGAS-STING axis, reviewing their potential clinical applications. Finally, we discuss key limitations of this new proposed therapeutic approach and provide possible techniques to overcome them.

cGAS-STING: a historical perspective

Our discovery and insight of the mechanisms and functions of the cGAS-STING DNA-sensing pathway could trace research on the innate antiviral immunity in early 1937, when virus interference is named based on the phenomenon that monkeys infected by one virus were protected from one another virus in an antibody independent way [11]. In 1957, Isaacs and Lindenmann conducted an elegant experiments, which revealed that cells treated with inactivated influenza virus produced a soluble factor that could protect fresh cells against subsequent infection with live virus [12]. They isolated and named this factor as"interferon" (IFN) for its ability to interfere with viral infection [13, 14]. The heated virus or a nucleic acid derived from cells not infected with viruses can induce IFN induction, indicating that foreign nucleic acid is the stimulus [11]. And now we know that the type I IFNs are a family of many closely related cytokines produced in response to virus infection [15].

After the discovery of NF-κB in the late 1980s, the transcriptional regulating cytokines was appreciated [16]. The interferon transcription factors (IRFs) family was identified as specialized transcription factors (TFs) to induce IFN [17, 18]. IFN induction mediated by the TBK1-IRF3 axis and NF-κB activation is the two hallmark events of viral infection [19]. Although the respective upstream sensors for nucleic acid remained unknown. Toll-like receptors (TLRs) are located on the cell membrane and expressed by sentinel immune cells that sample endosomal compartments for the presence of unusual nucleic acids, which cannot explain why all nucleated cells are responsible for viral infection with IFN production. There must exist a more ubiquitously expressed cytosolic sensor of nucleic acid.

The retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) were identified as the cytosolic dsRNA sensor in 2004 [20, 21]. Mitochondrial antiviral signaling (MAVS), the downstream adaptor of RIG-I, was identified in the 2005 [22–25], which now constitutes the RIG-I-MAVS pathway to detect RNA. The RIG-I pattern recognition receptor (PRR)-like receptors detect structural features of viral RNAs that are scarce within our own cells and signal through MAVS to activate the IFN-mediated antiviral response [26]. However, the sensor for cytosolic DNA is long missing. In 2006, two pioneer works revealed that transfection-introduced double-stranded DNA (dsDNA) into the cytoplasm induces type I IFN [27, 28], which agreed on the fact that the essential role of IRF3 is independent of TLRs, yet the dsDNA sensor remained to be determined. Eventually in 2008, the STING was identified as the adaptor for cytosolic DNA signaling [29, 30] (Fig. 1). Around the same time, study have shown that STING (there referred to as MPYS) is associated with major histocompatibility complex class II (MHC II) and involved in pro-apoptotic signalling [31]. Although all of the these pioneer studies reached a consensus that STING is a transmembrane protein, the exact membrane topology and subcellular location awaits further investigation. Subsequent studies revealed that STING is an ER-resident membrane passing molecule with its carboxy-terminal (C-terminal) part facing the cytosol [30, 32]. Functional studies have unrevealed that STING functions antiviral activity dependent of TBK1-IRF3, yet the respective upstream signal leading to its signaling function remains unclear.

Although STING was generally postulated to recognize DNA and RNA virus, a more pronounced phenotype was observed for synthetic dsDNA ligands and DNA viruses [29, 30]. In fact, AT-rich dsDNA or double-stranded RNA (dsRNA) STING-independently exerted antiviral activity via the RIG-I and PRRs MDA5, respectively [33]. In short, these studies indicated that STING maybe functions as the long-sought link between cytosolic DNA recognition and antiviral immunity, initially providing further strong support for the hypothesis that STING directly detects DNA itself [34]. However, later studies revealed that STING works as a receptor for bacterial cyclic dinucleotides, which resulting from its function in DNA recognition [35]. The pioneering work from Chen and colleagues soluted this conundrum with the discovery of cGAS, which acts as a direct DNA receptor and produces the endogenous cyclic dinucleotide second messenger molecule cGAMP to, in turn, activates STING [36, 37]. We refer readers to learn more detailed discussion of historical perspective on road to discovery of cGAS-STING for recent excellent reviews [2, 12, 38].

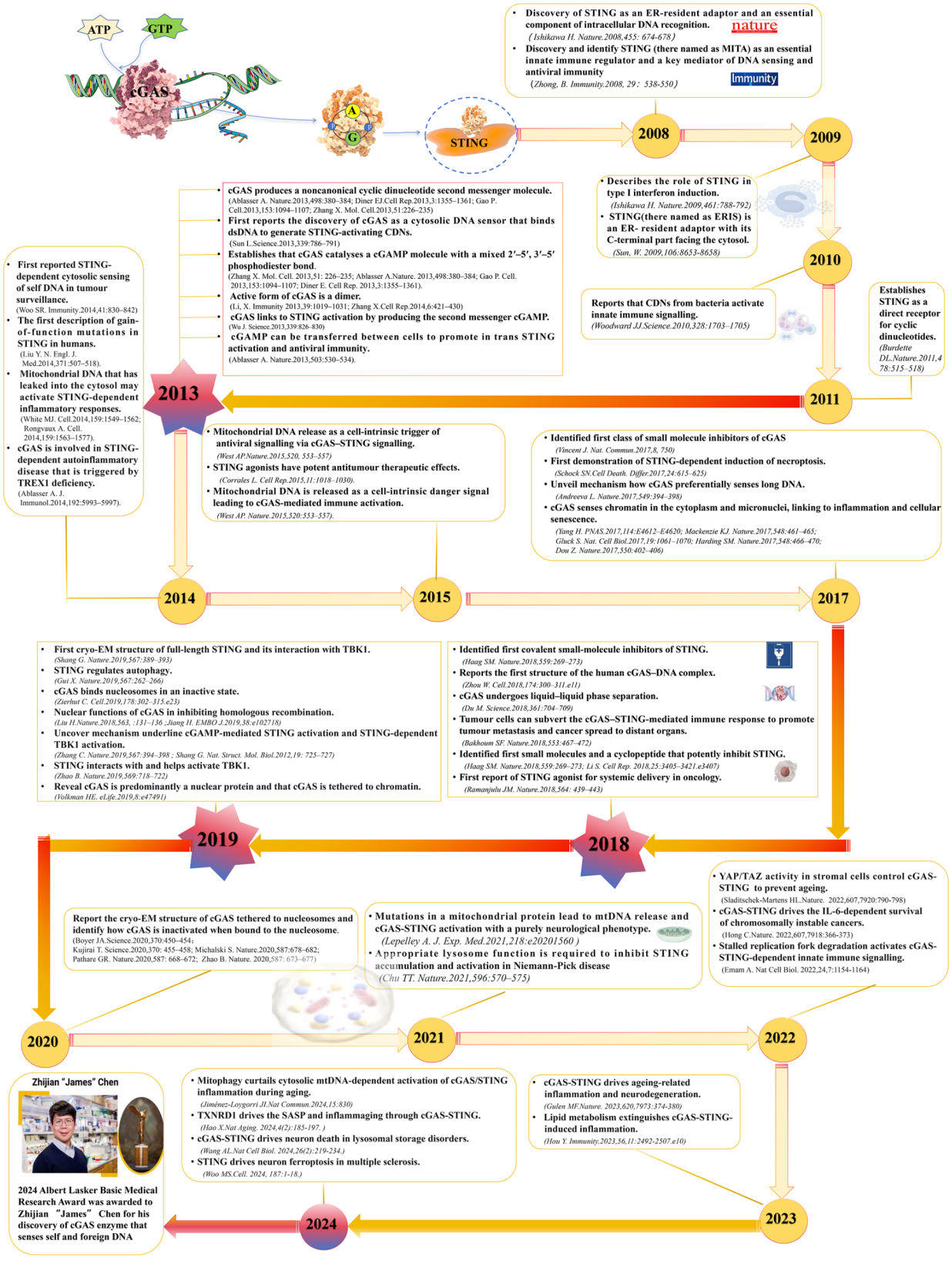

Fig. 1 Key Developments in cGAS-STING Research. Timeline depicting the scientific discoveries of the cGAS-STING pathway from 2008 to 2024

Overview of the cGAS-STING signaling axis

The DNA-sensing nucleotidyl transferase enzyme cyclic GMP/AMP (cGAMP) synthase (cGAS) is upstream of STING [36, 37]. The cGAS-STING signaling axis detects pathogenic extranuclear DNA and initiates a type I interferon innate immune activation, physiologically used against microbial infections, making cGAS-STING an integral component the innate immune response [39]. Belonging to a member of the nucleotidyl transferase (NTase) enzyme family, cGAS is also known as MB21D1 [39]. STING is otherwise known as endoplasmic reticulum interferon stimulator (ERIS) [32], N-terminal methionine-proline-tyrosine-serine plasma membrane transpanner (MPYS) [31, 40], mediator of interferon regulatory factor 3 (IRF3) activation (MITA) [29] or transmembrane protein 173 (TMEM173) [39]. The DNA sensor cGAS senses microbial (i.e. viral, bacterial, protozoal) double-stranded DNA (dsDNA), independent of sequence. cGAS may be activated by either endogenous DNA, mitochondrially-released DNA, or genotoxic stress-mediated extranuclear chromatin, placing cGAS-STING as a crucial signaling axis in autoimmunity, the sterile inflammatory response, and the induction of cellular senescence [39]. An overview of the cGAS-STING signaling axis is illustrated in Fig. 2. In mammalian cells, cGAS induces the synthesis of the secondary-messenger cyclic GMP/AMP (cGAMP), forming a crucial cytosolic DNA-sensing mechanism. cGAS binding to dsDNA induces a conformational change, activating it and initiating enzymatic activity [41–45]. Active cGAS catalyzes and converts guanosine triphosphate (GTP) and adenosine triphosphate (ATP) into 2′,3′-cyclic GMP-AMP (cGAMP) [37]. Subsequently, cGAMP binds to and activates STING, a ~40-kDa endoplasmic reticulum (ER)-localized transmembrane protein adaptor [30, 33, 37], to form homomeric quaternary ensembles of varying stoichiometry [46, 47]. After activation, STING translocates from the ER to the Golgi, where it recruits TANK binding kinase 1 (TBK1) and IκB kinase (IKK), which respectively phosphorylate interferon regulatory factor 3 (IRF3) and the nuclear factor-κB (NF-κB) inhibitor IκBα [39]. TBK1 transphosphorylates itself, the

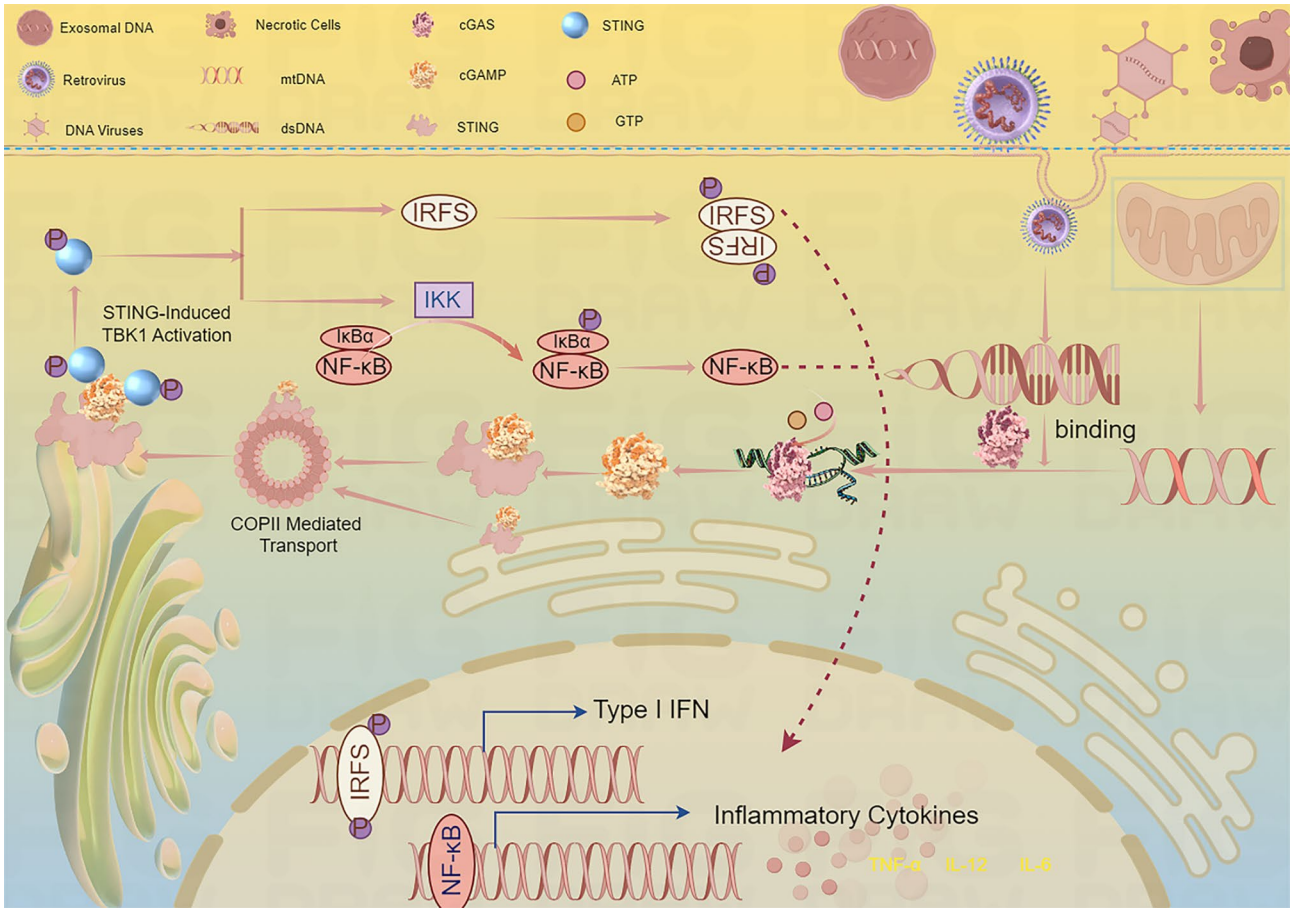

Fig. 2 The cGAS-STING Signaling Cascade. dsDNA (introduced by viral or extracellular origins) binds to cGAS catalyzing the synthesis of cGAMP. cGAMP upon binding ot STING transports to the Golgi where TBK1 transphosphorylation occurs. Phosphorylated TBK1 can then phosphorylate IRF3 inducing the nuclear transcription of IFN 1 genes or can activate IKK, inducing NF-kB mediated cytokine synthesis. STING is then recycled from the Golgi apparatus and degraded

C-terminal domains of STING, and subsequently IRF3 [39]. Meanwhile, STING engages and activates IKK to trigger NF-κB signaling [39], which works together with a robust IFN response to orchestrate the immunologically-driven clearance of intracellular bacteria, retroviruses, and DNA viruses [39]. IRF3 dimerizes and translocates to enter the nucleus, transcriptionally activating genes which encode type I interferons, such as interferon-β (IFNβ), initiating antiviral defense mechanisms [39]. The phosphorylation of IκBα leads to the nuclear translocation of NF-κB, enhancing the expression of proinflammatory cytokines such as tumour necrosis factor (TNF) and IL-6 [3]. STING is trafficked to endolysosomes for degradation after activation [39]. cGAS senses cytosolic dsDNA in response to tissue injury or pathogenic invasion, which allows for the cGAS-STING axis to regulate various cellular functions, such as protein synthesis, IFN/cytokine production, autophagy, senescence, metabolism, and specific mechanisms of cell death [39]. cGAS and STING are tightly regulated by transcriptional, post-translational, and protein degradation mechanisms, for which we refer readers to a specific review for further discussion [39]. The cGAS-STING axis contributes to tissue homeostasis and host defense, while dysfunction of cGAS-STING activates pro-inflammatory signaling pathways, resulting in inflammatory, autoimmune, degenerative diseases, and cancers [39].

cGAS-STING in lung diseases

Acute lung injury

Growing experimental evidence implicates that cGAS-STING axis drives the pathogenesis of acute lung injury. Increased plasma mtDNA activates cGAS-STING pathway to drive neutrophil infiltration in burn-induced rats with acute lung injury [48](Fig. 3). Hemorrhagic shock (HS)-induced release of extracellular cold-inducible RNA-binding protein (eCIRP) recognizes TLR4 as its receptor to activate STING, TBK1, and IRF3 via MyD88-dependent or -independent pathway using toll/IL-1 receptor (TIR) domain-containing adapter-inducing IFN-β (TRIF). Through the TLR4-MyD88 axis, eCIRP promotes mtDNA release, which stimulates cGAS/STING and induces the expression of IFN-α/b, thereby promoting tissue damage and inflammation in HS. Together, HS enhances the release of eCIRP, which agonizes STING and promotes the synthesis of IFN-1, thereby contributing to tissue injury and acute lung

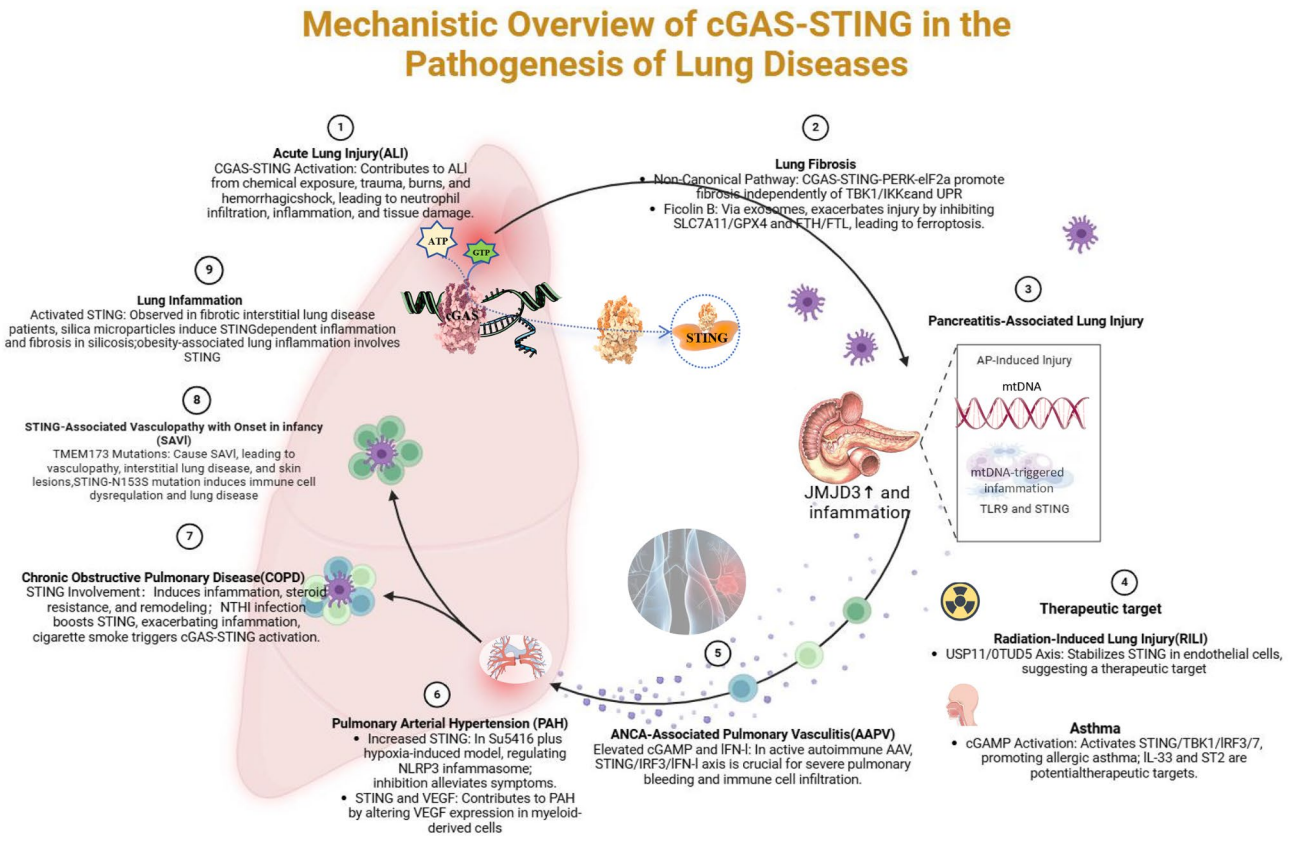

Fig. 3 Mechanistic Overview of cGAS-STING in the Pathogenesis of lung diseases. cGAS-STING contributes to the pathogenesis of Acute lung injury, Lung fibrosis, Pancreatitis-associated lung injury, Radiation-induced lung injury, Asthma, AAPV, Pulmonary arterial hypertension, Chronic obstructive pulmonary disease, STING-associated vasculopathy with onset in infancy (SAVI), and Lung inflammation

injury [49]. Activation of the STING/IRF3 axis drives paraquat (PQ)-induced acute lung injury [50].

The gasdermin D (GSDMD) facilitates neutrophil extracellular traps (NETs) by activating mtDNA-cGAS-STING pathway in lung ischemia/reperfusion(I/R) [51]. GSDMD promotes mtDNA leakage into the neutrophil cytosol, which activates the cGAS-STING axis and promotes NET formation in lung I/R. Pharmacological inhibition of the cGAS-STING axis by H-151 prevents cytosolic mtDNA-driven NET synthesis [51]. Both mtDNA and oxidized mtDNA promote NET synthesis, sterile inflammation, and lung injury in bleomycin-exposed mice, where oxidized mtDNA is more potent than non-oxidized mtDNA. mtDNA further promotes neutrophil activity through cGAS-STING and Toll-like receptor 9 (TLR9) axis, promoting neutrophil elastase and extracellular neutrophil-derived DNA in NETs [52].

Emerging studies have revealed that activation of the cGAS-STING axis contributes to the pathogenesis of sepsis-associated acute lung injury (Fig. 4). Dysregulated alveolar macrophages can promote acute lung injury. Recent study has shown that monocyte-derived macrophages ($CD11b^+$ macrophages) recruited into the airspace facilitate the anti-inflammatory functionality of alveolar macrophages by suppressing STING signaling [53]. Loss of $CD11b^+$ macrophages shifts the alveolar macrophage population towards a more inflammatory variety, enhancing neutrophil trafficking, lethality, and irreversible loss of lung vascular barrier function in LPS-induced mice [53]. Mechanistical study showed that $CD11b^+$ macrophages suppress STING through sphingosine kinase-2 (SPHK2)-mediated production of sphingosine-1-phosphate (S1P) in alveolar macrophage [53]. These results suggested that STING promotes pro-inflammatory activity of alveolar macrophages in sepsis-associated acute lung injury, while SPHK2-synthesized S1P in $CD11b^+$ macrophages prevent STING activity and suppress sepsis-associated acute lung injury [53]. These data were supported by later study from same group, who revealed that depletion of $CD11b^+$ monocytes results in mortality of mice through the persistent inflammatory injury, neutrophils infiltration, STING signaling activation in LPS-induced mice [54]. Recent evidence suggests that STING is involved in progression of sepsis-associated acute lung injury via the cytosolic DNA-STING-NLRP3 axis [55]. The increased expression of STING and phosphorylated STING has been found in primary macrophages and lung tissue in LPS-treated mice. STING loss attenuates oxidative stress and inflammation and abolishes NLRP3 inflammasome activation-mediated pyroptosis in LPS-treated murine lungs and macrophages [55]. NLRP3 overexpression attenuates the STING knockout-mediated protective effects in LPS-treated macrophages [55]. LPS increased cytosolic

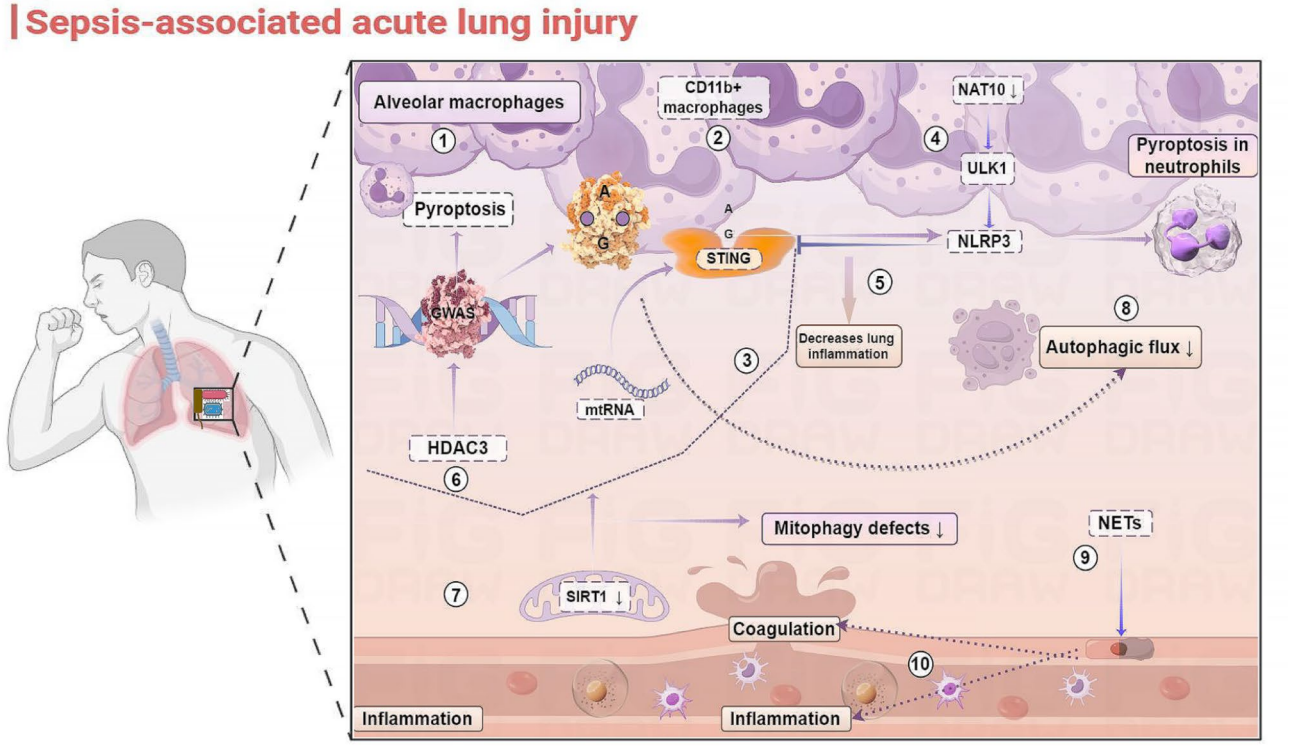

Fig. 4 Mechanistic Overview of cGAS-STING in the Pathogenesis of sepsis-associated acute lung injury. cGAS-STING is pathogenic in sepsis-associated acute lung injury, in which many disease-specific regulators modify pathway activity

mtDNA in macrophages. Exogenous mtDNA enhances STING phosphorylation, pyroptosis, inflammation, and oxidative stress in macrophages without influencing to the level of STING. Inhibition of cGAS inhibits sepsis-associated acute lung injury by suppressing the STING/NLRP3 axis activity [55]. cGAS inhibition also decreases LPS-induced cGAMP generation, indicating that the mtDNA-cGAS-STING-NLRP3 axis is independent of STING concentration [55]. LPS increases expression of c-Myc, which transcriptionally upregulates STING expression without affecting its phosphorylation [55]. Together, these results suggests that LPS induces sepsis-associated acute lung injury through c-Myc-dependently upregulating STING and cytosolic mtDNA-dependently activating STING, highlighting the cytosolic mtDNA-STING-NLRP3 axis as a novel therapeutic target against sepsis-associated acute lung injury [55]. The decreased N-acetyltransferase 10 (NAT10), an acetyltransferase which N^4-acetylates cytidine (ac4C) in mRNA, promotes sepsis-associated acute lung injury by inducing pyroptosis and the neutrophil ULK1-STING-NLRP3 axis [56]. NAT10 repression promotes the degradation of ULK1 transcripts, promoting STING-IRF3-NLRP3 activity in neutrophils and sepsis-associated acute lung injury. NAT10 overexpression in neutrophil attenuates septic lethality in mice by suppressing pyroptosis through reversing the ULK1-STING-NLRP3 axis [56]. Decreased NAT10 in sepsis patients correlates with clinical severity. These results suggest that NAT10 works as a pyroptosis inhibitor through inhibiting ULK1-STING-NLRP3 axis in neutrophils, thereby suppressing sepsis-associated acute lung injury [56]. The non-inflammasome member NLR family CARD domain-containing 3 (NLRC3) negatively regulates STING. NLRC3 overexpression decreases lung inflammation in LPS-treated mice. Silencing NLRC3 aggravates sepsis-associated acute lung injury [57]. Upregulated histone deacetylase 3 (HDAC3) has been observed in the lungs from LPS-treated mice. Macrophage HDAC3 knockout prevents sepsis-associated acute lung injury in LPS-treated mice. Silencing HDAC3 suppresses cGAS-STING in LPS-primed macrophages. LPS recruits HDAC3/H3K9Ac to the promoter of miR-4767 gene, repressing its transcription and upregulating cGAS [58]. Together, these data suggest that HDAC3 promotes sepsis-associated acute lung injury by inducing macrophage pyroptosis via the cGAS-STING axis [58]. Sirtuin 1 (SIRT1), a histone protein deacetylase, inhibits sepsis-induced acute lung injury [59]. Silencing SIRT1 enhances cytosolic release of mtDNA, which triggers NLRP3 inflammasome and STING over-activation by interfering with mitophagy through late endosome Rab7, leading to the accumulation of damaged mitochondria [59]. Ablation of SIRT1 promotes sepsis-induced acute lung injury by activating STING-NLRP3 axis through interfering with mitophagy [59]. Increased CD40L was observed in the plasma of CLP mice. Ablation of CD40L suppresses the activation of DC cells and Th17 differentiation while enhances the Th2 differentiation. The mechanistic study indicates that CD40L facilitates the activation of cGAS-STING pathway [60].

Recent evidence has revealed that circulating mtDNA-mediated STING activation promotes sepsis-associated acute lung injury by attenuating sepsis-related autophagic flux [61]. Increased activity of mtDNA-STING has been observed in patients with sepsis-induced acute lung injury. mtDNA mediates lung injury by inducing inflammation and preventing autophagy through STING activity. STING activation, in an IFN-dependently manner, injures lysosomal acidification without preventing autophagosome synthesis or fusion, aggravating sepsis. STING deficiency or the promotion of autophagy attenuates lung injury [61]. Increased levels mtDNA in circulation are significantly correlated with the incidence and severity of sepsis-associated acute lung injury in septic patients. Increased circulating mtDNA enhances sepsis-associated acute lung injury by activating STING, thereby promoting dysfunction of lysosomal acidification and impaired autophagy [55]. Abnormally STING activiation leads to autophagic flux blockade through TBK1-dependently suppressing lysosomal acidification, resulting in a vicious cycle and sepsis-associated acute lung injury. These results suggest that STING activation initiate autophagy and STING-TBK1 injures function of autolysosome degradation, highlighting the targeting of mtDNA or the STING pathway as a novel therapy for sepsis-associated acute lung injury [55].

Neutrophil extracellular traps (NETs) result in immunologic response to injury, inflammation, and coagulation, all of which contributes to the pathogenesis of sepsis-associated acute lung injury [62]. Recent study reveals that NETs induce endothelial cell damage through activating STING to produce tissue factor (TF), leading to increased dysregulated coagulant and inflammatory responses and poor prognosis in sepsis-associated acute lung injury mice [62]. Disruption of NETs or inhibition of STING improves the prognosis of septic mice through reducing the inflammation and coagulation. Together, these results indicate that NETs mediate correlation between coagulation and inflammation through STING-dependently activating coagulant cascade in endothelial cells to promote sepsis-associated acute lung injury [62]. This observation was corroborated by recent study, which reports that NETs facilitate sepsis-associated acute lung injury through the cGAS-STING axis, highlighting a new therapeutic target for sepsis-associated acute lung injury [63].

Lung fibrosis

Recent study has revealed that a non-canonical cGAS/STING/PERK/eIF2α axis promotes pulmonary and renal fibrosis independent of the unfolded protein response (UPR), autophagy, and TBK1/IKKε [64]. cGAMP/STING/PERK/TBK1/IRF3 axis activity is not reliant upon the unfolded protein response [64]. Activated PERK phosphorylates eIF2α, thereby promoting a pro-inflammatory translation program that supports STING-dependent senescence and pulmonary fibrosis, provide a novel therapeutic target against fibrotic diseases [64]. Intra-exosomal Ficolin B within alveolar macrophages (AMs) exacerbates bleomycin-induced lung injury by promoting cGAS-STING- triggered ferroptosis by inhibiting SLC7A11/GPX4 and FTH/FTL in epithelial cells [65],. Nanoplastics (NPs), a common type of degraded plastic material associated with pulmonary injury, promotes oxidative stress, cell death, inflammation, and the activation of cGAS-STING pathway in RAW264.7 cells [66]. NPs induce pulmonary fibrosis, inflammation, apoptosis, and necrosis in vivo through activating cGAS-STING pathway [66].

Chronic obstructive pulmonary disease (COPD)

STING is involved in the pathogenesis of COPD, which is characterized by a slow progressive and irreversible inflammatory disease with steroid resistance, and remodeling [67]. Nontypeable Haemophilus influenzae (NTHI) infection boosts STING expression in COPD mice. NTHI and NTHI DNA upregulates the expression of IFN-β and CXCL10. STING/TBK1/IRF3 knockout or overexpression decreases or increases IFN-β/CXCL10 expression post-NTHI and -NTHI DNA exposure [68]. cGAS promotes NTHI and NTHI DNA-induced IFN-1 responses. Cumulatively, NTHI DNA functions as a PAMP to trigger the IFN-1 response through cGAS-STING axis. Internalized NTHI derived cytosolic DNA triggers IFN-β expression through the cGAS-STING-IFN-1 axis [68]. Cigarette smoke exposure strongly induces COPD. Cigarette smoke promotes respiratory damage and the release of dsDNA, activating cGAS/STING/IFN-1 lung inflammation in mice [69]. Loss of cGAS, STING or IFNAR attenuate lung inflammation in mice. Together, these results suggest cigarette smoke-induced dsDNA/cGAS/STING/IFN-1 could serve as a therapeutic target against COPD [69].

Pancreatitis-associated lung injury

Acute pancreatitis (AP) is complicated by inflammatory lung injury. mtDNA, oxidized-mtDNA, and upregulated JMJD3 expression have been observed in the lungs of L-arginine (L-Arg) and caerulein (Cae) AP male mouse and in patients with AP. mtDNA or oxidized-mtDNA promotes JMJD3 and proinflammatory effects [70]. mtDNA, oxidized-mtDNA-triggered AP and JMJD3 were prevented by STING/TLR9 knockout in the Cae-induced mice, suggesting that mtDNA and oxidized-mtDNA upregulate JMJD3 in monocytes and tissues through STING/TLR9 pathways [70]. JMJD3 inhibition prevents AP-induced pulmonary inflammation. Silencing the TLR9/STING pathways or JMJD3 inhibition alleviates AP-associated lung injury [70]. A recent study substantiates previous indications that STING promotes macrophage apoptosis, specifically regulating macrophage phenotypes in severe AP-associated lung injury [71].

Radiation-induced lung injury(RILI)

Upregulation of cGAS-STING axis activity has been observed in both mouse models and clinical lung tissues following irradiation exposure. Silencing cGAS or STING alleviates fibrosis and inflammation in mouse lung tissues. Loss of STING suppresses NLRP3 inflammasome and pyroptosis [72]. IRF3 promotes pyroptosis by inducing the expression of NLRP3. Radiation therapy enhances the release of self-dsDNA to activate cGAS-STING and NLRP3-mediated pyroptosis [72]. These results suggest that radiation induces lung injury occurs via activation of the cGAS-STING pathway, which in turn activates NLRP3-mediated pyroptosis [72]. Additionally, radiation promotes the release of damaged DNA, which activates macrophage STING, contributing to macrophage polarization/recruitment in the lung, thereby inducing RILI [73]. Inhibition of USP11 alleviates RILI, as evidenced by decreased apoptosis, reduced pulmonary vessels permeability, and diminished infiltration of neutrophils and macrophages, along with increased endothelial cell proliferation in lung [74]. USP11 stabilizes the deubiquitinating enzyme OTUD5 by reducing OTUD5 K48-linked ubiquitination, which in turn stabilizes STING and mediats RILI. Together, these results suggest that USP11/OTUD5 axis induces RILI through stabilizing STING in endothelial cells [74].

Pulmonary arterial hypertension

Increased STING expression has been observed in SU5416 plus hypoxia (Su/Hy)-induced rat models of pulmonary arterial hypertension (PAH) [75]. STING regulates NLRP3 expression, and its inhibition alleviates inflammation and pulmonary artery pressure [75]. Cumulatively, STING mediates PAH by promoting macrophage-driven NLRP3 inflammation. Another study supports this finding, reporting that STING contributes to PAH development by altering of VEGF expression in myeloid-derived cells, independent of IFN-1 signaling [76]. A recent study elaborates on this finding, demonstrating that STING contributes to PAH by targeting Interferon and bone morphogenetic protein receptor 2

(BMPR2) signaling through regulation of coagulation factor II (thrombin) receptor-like 3 (F2RL3) [77].

Lung inflammation

Activated STING is found in the lungs of patients with fibrotic interstitial lung disease (ILD) [78]. Streptococcus pneumoniae-derived hydrogen peroxide induces mtDNA release, promoting IFN-1 responses via STING in lung cells [79]. cGAS-STING promotes the MyD88 pathway in monocytes, leading to IFNγ secretion during pneumococcal infection [80]. Activation of the STING axis may also contributes to the genesis of Sjögren's Syndrome (SS) with concomitant lung and salivary gland disease [81]. Pulmonary disorders are characterized by high rates of comorbidity with metabolic disorders. STING expression and STING-induced inflammation are enhanced in the lungs of obese patients [82]. STING inhibition prevents the obesity-induced lung inflammation. STING promotes PA-induced inflammation through the STING/TBK1 /IRF3/NF-κB axis in the lung macrophages [82].

Asthma

cGAMP is a type 2 adjuvant that aids in inducing allergic asthma, specifically by agonizing the STING/TBK1/IRF3/7 axis. Thus, IL-33 and the IL-33 receptor (ST2) can be viewed as novel targets for the treatment of treat allergic asthma [83].

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated pulmonary vasculitis (AAPV)

Increased cGAMP and IFN-I are associated with patients experiencing active autoimmune AAV [84]. The STING/IRF3/IFN-I axis is essential for immune cell infiltration, pulmonary bleeding, and lung pathology in anti-MPO monoclonal antibodies-treated C57BL/6J mice to induce ANCA pulmonary autoimmune vasculitis [84].

STING-associated vasculopathy with onset in infancy (SAVI)

STING-associated vasculopathy with onset in infancy (SAVI) is characterized by interstitial lung disease, vasculopathy, premature death, and ulcerative skin lesions. Primarily it is an autoinflammatory disease caused by gain-of-function mutations in TMEM173 that encodes STING [85]. SAVI-associated STING with N153S activates IRF3-independent immune cell dysfunction and lung disease in mice [86, 87], which additionally promotes IFN-1-independent T cell impairment [88]. SAVI-associated STING with de novo mutation p.Arg284Ser triggers IFN-gene activation similar to that of interferonopathy without elevated systemic inflammatory markers or cutaneous vasculitis [89]. SAVI-associated STING due to missense mutations at 206, 281, and 284 allows for cGAMP-independent IFN-1 activity, which was prevented by the administration of the janus kinase 1/2 inhibitor ruxolitinib [90].

Lung silicosis

Increased dsDNA and CXCL10 in sputum have been found in patients with silicosis [78]. Silica microparticles are cytotoxic, inducing dsDNA leakage, inflammation via the STING-IFN-1 axis, and CXCL10 expression in the airways of mice [78]. cGAS further contributes to STING activity after silica-exposure. DNase I-induced dsDNA catabolism prevents silica-induced STING-mediated IFN-1 activity and subsequent lung inflammation. Thus, the dsDNA-cGAS-STING pathway promotes silica-induced lung inflammation, while DNase I prevents this response [78]. This observation was corroborated by another study, which reports silica particles drive the dsDNA/STING activity, contributing to inflammatory resposnes in alveolar macrophages [91]. Ablation of STING prevents the inflammatory and fibrotic macrophage response to alleviate silicosis [91].

Therapeutic potential of cGASSTING inhibition in lung diseases therapy

Several compounds have already demonstrated therapeutic potential by targeting cGAS-STING in lung diseases (Fig. 5). A summary of compounds functions as cGAS-STING inhibitors are itemized in Table 1; Fig. 6.

Acute Lung Injury

Oral and intranasal administration of the TBK1 inhibitor amlexanox reduces lung allergic inflammation in cGAMP-induced female C57BL/6J mice [83]. C-176 inhibits pulmonary apoptosis and pyroptosis in mice with intestinal ischemia-reperfusion injury. The anti-apoptotic and anti-pyroptotic effects of C-176 against acute lung injury were reversed by compound C in mice exposed to IR [107]. C-176 attenuates intestinal ischemia-reperfusion-mediated acute lung injury through activating AMPK. These results suggest that STING-pyroptosis pathway is involved in the genesis of acute lung injury [107]. The cGAS inhibitor RU.521 attenuates ERS, thereby alleviating inflammatory response, oxidative stress and apoptosis in alveolar epithelial type II cells, while promoting pulmonary ventilation function in I/R rats. The potent STING agonist SR-717 aggravates ERS and lung injury in an I/R SD rat model [108]. A GSDMD inhibitor disulfiram reduces pathological injury and NETs release in lung I/R, both in vivo and in vitro [51]. C176 alleviate lung injury and sepsis severity. C176 improves barrier function, reduces serum levels of IL- 6, IL-1β, and TNF-α and alleviates inflammatory changes as well as lung MPO activity [59]. A small molecule SIRT1 activator SRT-1720 alleviates sepsis severity, improves barrier function, reduces activation of the NLRP3 and

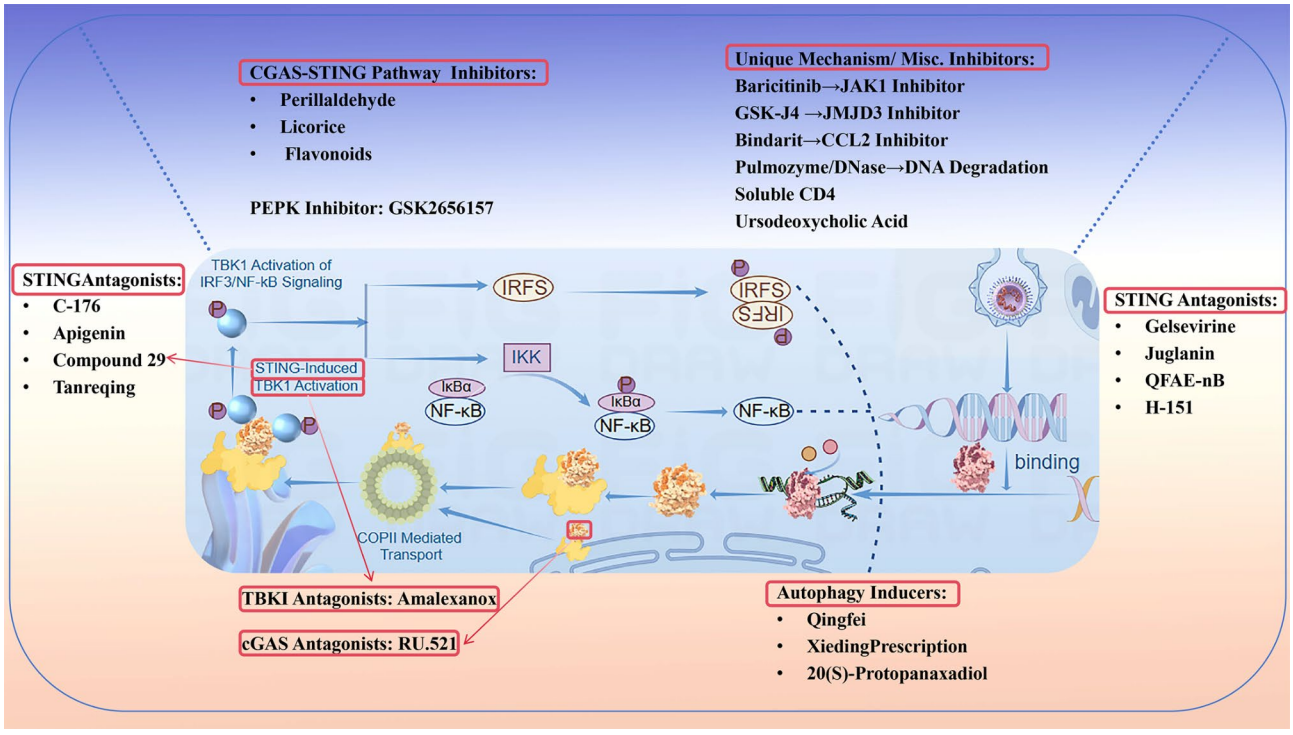

Fig. 5 cGAS-STING Pathway Antagonists in the Setting of lung diseases. Multiple classes of cGAS-STING antagonists have shown benefit against lung diseases models. (1).Activation of cGAS-STING is implicated in the pathogenesis of sepsis-associated acute lung injury (ALI), mediated by dysregulated alveolar macrophages. (2). CD11b + macrophages inhibit STING signaling, suppressing inflammation in ALI. Loss triggers inflammatory macrophage expansion, neutrophil accumulation, and vascularbarrier dysfunction. (3). STING participates in ALI development via cytosolic DNA-STING-NLRP3 axis, with LPS-induced mitochondrial DNA release activating STING and NLRP3 infammasome. (4). NAT10 downregulation promotes ULK1-STING-NLRP3 axis, facilitating pyroptosis in neutrophils, contributing to ALI progression. (5). NLRC3 negatively regulates STING, its overexpression decreases lung inflammation in LPS-treated mice. (6). HDAC3 mediates macrophage pyroptosis by activating cGAS-STING, suggesting a potential therapeutic target for ALI. (7). SIRT1 deficiency aggravates ALI due to mitophagy defects and NLRP3/STING hyperactivation, highlighting its role in regulating mitochondrial sianals. (8). Circulating mtDNA-mediated STING activation obstructs autophagic flux, exacerbating ALI in sepsis patients. (9). NETs induce endothelial cell damage via STING activation, magnifying dysregulated coagulation and inflammation in sepsis-associated All. (10). Inhibition of STING or disruption of NETs improves prognosis by reducing inflammation and coagulation, suggesting a potential therapeutic strategy for ALI

STING signaling pathways, and decreases lung injury and inflammatory changes and lung MPO activity [59].

Apigenin (4,5,7-trihydroxyflavone), a natural flavonoid found in fruits, vegetables, and Chinese medicinal herbs, possesses antibacterial and anti-inflammatory activities. Apigenin functions as a potent agent to reduce the synthesis of type I interferons (IFNs) [95]. Apigenin mitigates lung inflammation and edema in LPS-induced mice. Apigenin attenuates inflammation through inhibiting the activation of the STING-IRF3 pathway both in vitro and in vivo [95]. The STING agonist SR-717 reverses the inhibitory effects of apigenin in LPS-induced THP1-Blue™ ISG macrophages [95]. Mechanistical studies have showed that apigenin downregulates STING-mediated IFN beta 1 (IFNB1) expression by inhibiting STING expression, reducing dimerization and the nuclear translocation of phosphorylated IRF3, and disrupting the association of STING with IRF3. Collectively, apigenin alleviate LPS-induced acute lung injury by inhibiting STING/IRF3 pathway [95]. Perillaldehyde alleviates LPS-induced acute lung injury by inhibiting cGAS-STING-mediated IRF3-NF-κB signaling [96]. LDK378 improves survival rate of SD rats through reducing septic acute lung injury [118]. These results were corroborated by other studies, which reported that LDK378 decreases alveolar septal wall thickening, leukocyte infiltrates, alveolar congestion and edema, as well as mRNA expression of IFNβ, TNFα, monocyte chemoattractant protein-1 (MCP1), and IL-7 in CLP/C57BL/6J mice [100]. Inhibition of the ALK-STING pathway reduces septic acute lung injury [100]. As active ingredients extracted from the Chinese herb licorice, Licorice flavonoids possess anti-inflammatory, antioxidant, gastroprotective, antitumor, and antibacterial pharmacological effects [119]. Licorice flavonoids inhibit activation of the cGAS-STING pathway, as evidenced by decreased expression of type I interferons, SG15, C-X-C motif chemokine ligand 10 (CXCL10), IL-6 and TNF-α [98]. Licorice flavonoids inhibits septic acute lung injury through inhibiting activation of cGAS-STING signaling pathway via

Table 1 Emerging compounds targeting cGAS-STING to attenuate lung diseases

Diseases	Compounds	Experimental model	Findings	Ref
ALI	Compound 30d-S	Male C57BL/B6/LPS	↓Alveolar obstruction, alveolar wall thickening, and neutrophil and erythrocyte exudation;↓wet/dry weight of the lung tissue;↓cell number and protein levels in BALF;↓protein phosphorylation of TBK1 and STING;↓ production of IFN-β, mRNA expression of IFN-β, and ISG;↓secretion of inflammatory factors TNF-α, IL-6, and IL-12 in BALF supernatants, serum, and lung tissue.	[92]
ALI	C-176	Male C57BL/6J mice/LPS	↓Expression of STING;↓production of inflammatory cytokines(TNF-α, IL-6, IL-12, and IL-1β);↓expression of chemokines and adhesion molecule vascular cell adhesion protein-1 (VCAM-1).	[93]
ALI	C176	C57BL/6J male mice/CLP	↓Lung injury severity;↓sepsis severity;↑barrier function;↓serum levels of IL-1β, IL- 6, and TNF-α;↓ inflammatory changes;↓MPO activity.	[59]
ALI	H-151	HMEC-1cells/TNF-α	↓Expression levels of adhesion molecule and chemokines;↓adhesive ability and chemotaxis of immunocytes; ↓phosphorylation of transcription factor STAT1.	[93]
ALI	H-151	Male C57BL/6 mice/LPS	↓Inflammatory lung injury.	[63]
ALI	H-151	C57BL/6J/LPS/CLP	↓Lungs tissue injury and fibrosis;↓injury scores;↓lung wet/dry ratio;↓infiltration of inflammatory cells;↓fibrinogen deposition in lung tissues;↓cytokine production;↓PT and APTT;↓activation of the STING; ↓TF expression.	[62]
ALI	Compound 29	BALB/c mice/LPS	↓ALI;↑lung tissue integrity;↓macrophage activation;↓nuclear translocation of IRF3 and p65;↓ STING/IRF3/NF-κB;↓inflammatory response;↓IL-6, TNF-α, and IFN-β.	[94]
ALI	Apigenin	BALB/c mice/LPS	↓Pathological pulmonary inflammation and lung edema;↓activation of the STING/IRF3 pathway.	[95]
ALI	SRT-1720	C57BL/6J male mice/CLP	↓Sepsis severity;↑arrier function;↓ NLRP3 and STING signaling pathways activation;↓lung injury and inflammatory changes;↓lung MPO activity.	[59]
ALI	Perillaldehyde	Female C57BL/6J mice /LPS	↓Lung histological changes;↓inflammatory cell infiltration;↓overproduction of inflammatory cytokines; ↓oxidative stress;↓the expression of cGAS, STING, p-TBK, p-IRF3, p-P65, and p-IκB.	[96]
ALI	Tanreqing		↓Lung edema and histological change;↓TNF-α, IL-6, IL-1β, and IFN-β;↓inflammatory cell infiltration; ↑SOD and GSH;↓ MDA, 4-HNE, LDH, and ROS;↓oxidative stress;↓cGAS, STING; ↓phosphorylated TBK, p65, pIRF3, and pIκBα.	[97]
ALI	Licorice flavonoids	Female C57BL/6J mice /LPS	↓Acute lung injury;↓activation of the cGAS-STING pathwa;↓expression of type I interferons;↓ISG15 and CXCL10; decreasesIL-6; decreasesTNF-α;↓cGAMP synthesis.	[98]
ALI	LDK378	C57BL/6J mice/CLP OR $STING^{-/-}$ mice CLP	↓Alveolar septal wall thickening;↓alveolar congestion and edema;↓leukocyte infiltrate;↓TNFα, IFNβ, MCP1, and IL-7 mRNA expression;↓ systemic release and accumulation in the serum.	[99]
ALI	LDK378	C57BL/6J mice/LPS	↓Organ dysfunction;↓Endotoxemic lethality;↓tissue injury;↓proinflammatory cytokine expression and release.	[99]
ALI	LDK378	Male SD rats/CLP	↑Survival rates;↓organ injuries; ↓perfused small vessel density;↑mean arterial pressure level;↓ microvascular flow index;↑expression of IL-10;↓expression of TNF-a and IL-6;↓phosphorylated TBK1 and phosphorylated IFR3 and phosphorylated p65.	[100]
ALI	Gelsevirine	Male C57BL/6J mice	↑Survival period;↓acute organ damage;↓2′3′-cGAMP-induced STING dimerization and subsequent activation;↑K48-linked ubiquitination and degradation of STING;↑upregulating and recruiting TRIM21.	[101]
ALI	Gelsevirine	2′3′-cGAMP; ISD; dA: dT /Raw264.7 and THP-1	↓Interferon and inflammatory cytokine induction in macrophages.	[101]
ALI	DNase I	C57BL/6J/CLP	↓Hemorrhage and alveolar edema;↓alveolar thickness;↓lung fibrosis;↓leukocyte infiltration;↓ inflammatory cytokine productio;↓fibrinogen deposition;↓PT and APTT;↓TF expression in the lung;↓STING activation.	[62]
ALI	DNase I	Male C57BL/6 mice/LPS	↓Expression of NETs and cGAS-STING.	[63]
ALI	Ursodeoxycholic acid	Male C57BL/6 mice OR $STING^{-/-}$ mice	↓Pulmonary edema;↓inflammatory cell infiltration;↓pro-inflammatory cytokines production;↓oxidative stress;↓damage of pulmonary barrier;↑alveolar fluid clearance;↓PANoptosis-like cell death (↓apoptosis, pyroptosis, and necroptosis); ↓STING pathway.	[102]
ALI	Soluble CD4	C57BL/6J/LPS	↓Lethal challenge; ↓TNF/IL-6.	[103]
ALI	Soluble CD4	C57BL/6J/CLP	↓Hyperinflammation similarly.	[103]

Table 1 (continued)

Diseases	Compounds	Experimental model	Findings	Ref
ALI	4-octyl itaconate	C57BL/6 male mice/LPS	↓Pulmonary edema, inflammatory cell infiltration, and production of inflammatory factors;↓ cleavage of gasdermin D (GSDMD), IL-18 and IL-1β release; ↓mitochondrial reactive ROS; ↓mtDNA release into the cytosol; ↓cGAS, STING expression, and IRF3 phosphorylation.	[104]
ALI	4-octyl itaconate	Murine alveolar macrophage cell line/LPS	↓cGAS, STING expression, and IRF3 phosphorylation; ↓STING/IRF3 pathway; ↓NLRP3-mediated pyroptosis.	[104]
ALI	RU.521	C57BL/6 J mice/ZnONPs	↓Activation of the cGAS-STING pathway; ↓oxidative stress and inflammation; ↓lung injury.	[105]
ALI	Dexamethasone	C57BL/6J mice/paraquat	↓Pathological changes and wet/dry ratios in lungs; ↓Sting, Irf3, and Ifnβ mRNA levels; ↓ STING and pIRF3 protein levels in lung tissues, and IFNβ secretion in serum; ↓IRF3 nuclear translocation.	[106]
ALI	C-176	Male C57BL/6 mice/I/R	↓Intestinal I/R-mediated ALI; ↑AMPK signal activation.	[107]
ALI	Disulfiram	C57BL/6 mice/I/R	↓NETs release; ↓lung pathological injury; ↓GSDMD caused mitochondrial DNA (mtDNA) leaking into the neutrophil cytosol, and then the cytoplasmic mtDNA activated the cGAS-STING signaling pathway and stimulated NETs formation in lung I/R.	[51]
ALI	RU.521	SD rats/I/R	↓Lung ischemia/reperfusion injury; ↓cGAS-STING; ↓endoplasmic reticulum stress in alveolar epithelial type II cells.	[108]
Fibrosis	QFAE-nB	C57BL/6 mice/bleomycin	↓Lung fibrosis; ↓activation of the STING; ↓signal transduction of TBK1-IRF3 and TBK1-NF-κB; knockout of the TREX1 gene caused massive inflammation and even induced PF in the lung tissues, whereas QFAE-nB effectively alleviated inflammation and reduced PF.	[109]
Fibrosis	Qingfei xieding prescription	Male SD rats/bleomycin	↓Pulmonary fibrosis; ↓mortality; ↓mtDNA-cGAS-STING inflammation pathway.	[110]
Fibrosis	Qingfei xieding prescription	Lung epithelial MLE-12 cells/TGF-β1	↓Expression of α-SMA and Collagen I; ↑cell viability; ↓lipid oxidation; ↓ROS contents; ↓mitochondrial damage; ↓TGF-β-mediated downregulation in autophagy; ↓mtDNA-cGAS-STING and inflammatory signaling.	[110]
Fibrosis	Tanreqing injection	Female C57BL/6 mice/bleomycin	↓Lung edema and pulmonary function; ↓inflammatory cell infiltration in BALF and inflammatory cytokines release (TNF-α, IL-6, and IL-1β) in serum and lung tissues; ↓collagen synthesis and deposition; ↓pulmonary fibrosis; ↓STING, p-P65, BIP, p-PERK, p-eIF2α, and ATF4 expression.	[111]
Fibrosis	GSK2656157	Male C57BL/6 J mice/bleomycin	↓Activation of PERK-eIF2α signaling; ↓fibrotic process; ↑alveolar structures ↓expression of collagens and lower fibrosis scores.	[64]
Fibrosis	Fluvoxamine	Male C57BL/6 mice/bleomycin	↑Pulmonary function; ↓expression of inflammatory factors; ↓excessive production of extracellular matrix; ↓lung fibrosis.	[112]
Fibrosis	Fluvoxamine	NIH/3T3/TGF-β1	↓cGAS-STING; ↓ activation of PERK/eIF2α/c-Myc/miR-9-5p/TBPL1 and TBK1/YAP/JNK1/2/Bnip3/CaMKII/cofilin signaling; ↓ activation and migration of fibroblasts.	[112]
Fibrosis	PPD	Male C57BL/6 mice/bleomycin	↑Survival rate; ↓ α-SMA, TGF-β1 and collagen I; ↓STING levels that was reduced by phosphorylated AMPK after activation by PPD.	[113]
Fibrosis	Juglanin	Male C57BL/6 mice/bleomycin	↑Survival rate; ↓neutrophil alveolar infiltration, lung vascular permeability and pro-inflammatory response; ↓pulmonary fibrosis; restraines STING.	[114]
Fibrosis	Heterophyllin B	Male C57BL/6 mice/bleomycin	↑AMPK phosphorylation and reduces STING; ↓damaged lung tissue; ↓alveolar epithelial mesenchymal transition (EMT); ↓ lung fibroblast transdifferentiation.	[115]
Pancreatitis-Associated Lung Injury	C-176	Mlice/caerulein + LPS	↓Lung injury and inflammation.	[71]
Pancreatitis-Associated Lung Injury	GSK-J4	Mlice/caerulein + LPS	↓Lung pathological lesions; ↓percentage of TNF-a1CD451CD11b1Ly6C1 inflammatory monocytes in the lung, and peripheral blood.	[70]

Table 1 (continued)

Diseases	Compounds	Experimental model	Findings	Ref
AAPV	H151	C57BL/6J mouse anti-MPO IgG + fMLP and LPS	↓Vasculitis-associated weight loss; ↓incidence of mice with pulmonary hemorrhages; ↓leukocyte infiltration in the BAL.	[84]
AAPV	Baricitnib	C57BL/6J mouse anti-MPO IgG + fMLP and LPS	↓Weight loss and lung histopathology; ↓degree of developing hemorrhages.	[84]
Asthma	Amlexanox	Female C57BL/6J mice /cGAMP	↓cGAMP-induced lung allergic inflammation.	[83]
Inflammation	C-176	Male C57BL/6J mice /HFD	↓Obesity-induced lung inflammation.	[82]
PAH	C-176	SD rats/SU5416 plus hypoxia	↓Increased pulmonary artery pressure; ↓activation of the NLRP3 inflammasome and proinflammatory cytokines.	[75]
RILI	Bindarit	C57BL/6 mice/Gy	↓Recruitment and polarization of macrophages; ↓RILI.	[73]
RILI	Pulmozyme	C57BL/6 mice/Gy	↓RILI by degrading extracellular dsDNA; ↓cGAS-STING-NLRP3 signaling pathway.	[72]
Silicosis	Honokiol	male C57BL/6 N mice /Crystalline silica particles	↓Pulmonary fibrosis; ↓mitochondrial damage; ↓activation of the NF-κB signaling pathway.	[116]
Silicosis	Honokiol	A549/Silica	↓Senescence;↑sirt3 expression; ↓mtDNA damage; ↓cGAS expression.	[116]
Senescence	Selenomethionine	Male C57BL/6J mice/PM2.5	↓Aging of mouse lung tissue; ↓cGAS expression.	[117]
Senescence	Selenomethionine	A549 cells/PM2.5	↓Inflammatory response; ↓ cellular senescence; ↓ cGAS/STING/NF-κB.	[117]
Senescence	PF-06928215(cGAS)	A549 cells/PM2.5	↓Senescence and inflammatory response; ↓activation of cGAS/STING/NF-κB pathway.	[117]
Senescence	BAY 11-7082	A549 cells/PM2.5	↓Senescence and inflammatory response; ↓activation of cGAS/STING/NF-κB pathway.	[117]

AAPV, Anti-neutrophil cytoplasmic antibodies (ANCA)-associated pulmonary vasculitis; BALF, bronchoalveolar lavage fluid; Bindarit, CCL2 inhibitor; ZnONPs, Zinc oxide nanoparticles; Amlexanox, TBK1 inhibitor; PPD,20(S)-Protopanaxadiol; EX527, SIRT1 inhibitor; SRT-1720, a small molecule SIRT1 activator); PAH, Pulmonary arterial hypertension; RILI, Radiation-induced lung injury

blocking cGAMP synthesis [98]. The hederagonic acid derivative compound 29 suppresses septic acute lung injury through inhibiting activation of macrophage, decreasing the nuclear translocation of IRF3 and p65, and disrupting STING-IRF3-NF-κB pathway, thereby attenuating the inflammatory response [94]. As a Chinese patent medicine for respiratory-related diseases, Tanreqing inhibits septic acute lung injury through downregulating STING signaling pathway [97]. Gelsevirine functions as a novel specific STING inhibitor to attenuate septic acute lung injury [101]. Gelsevirine suppresses STING agonists-mediated interferon and inflammatory cytokine induction, and promotes TRIM21-mediated ubiquitination and degradation of STING. And H-151 [62], ursodeoxycholic acid [102], DNase I [62], and soluble CD4 [103] all inhibits septic acute lung injury through alleviating cGAS-STING pathway.

ARDS

4-octyl itaconate (4-OI) alleviates lung injury, as evidenced by decreased inflammatory cell infiltration, pulmonary edema, and production of inflammatory factors in LPS-treated C57BL/6 male ARDS mice. 4-OI prevents LPS-induced NLRP3-mediated pyroptosis both in vitro and in vivo. 4-OI inhibits oxidative stress-induced mtROS and mtDNA release to the cytosol in alveolar macrophages. Additionally, 4-OI downregulates the expression of cGAS and STING, and inhibits IRF3 phosphorylation in both in vitro and in vivo models. Inhibition of the STING/IRF3 pathway further attenuates LPS-induced NLRP3-mediated pyroptosis in vitro. Taken together, these results suggest that 4-OI alleviates ARDS through a STING/IRF3-dependent mechanism, inhibiting mitochondrial dysfunction and suppressing NLRP3-mediated pyroptosis in macrophages [104].

Fibrosis

Juglanin attenuates bleomycin-induced lung injury by inhibiting inflammation and fibrosis through suppression of STING signaling [114]. Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), improves pulmonary function, decreases the expression of inflammatory factors and excessive production of extracellular matrix, thereby alleviating lung fibrosis through inhibiting cGAS-STING in bleomycin-treated Male C57BL/6 mice [112]. Tanreqing injection attenuates bleomycin-induced lung edema and pulmonary dysfunction. It decreases bleomycin-induced inflammatory cytokines release in serum and lung tissues and inflammatory cell infiltration in BALF. It also alleviates bleomycin-induced pulmonary fibrosis and significantly prevents STING, p-P65, BIP, p-PERK, p-eIF2α, and ATF4 expression in lung fibrosis mice, suggesting Tanreqing inhibits pulmonary fibrosis through inhibiting STING-mediated ERS(ER stress)

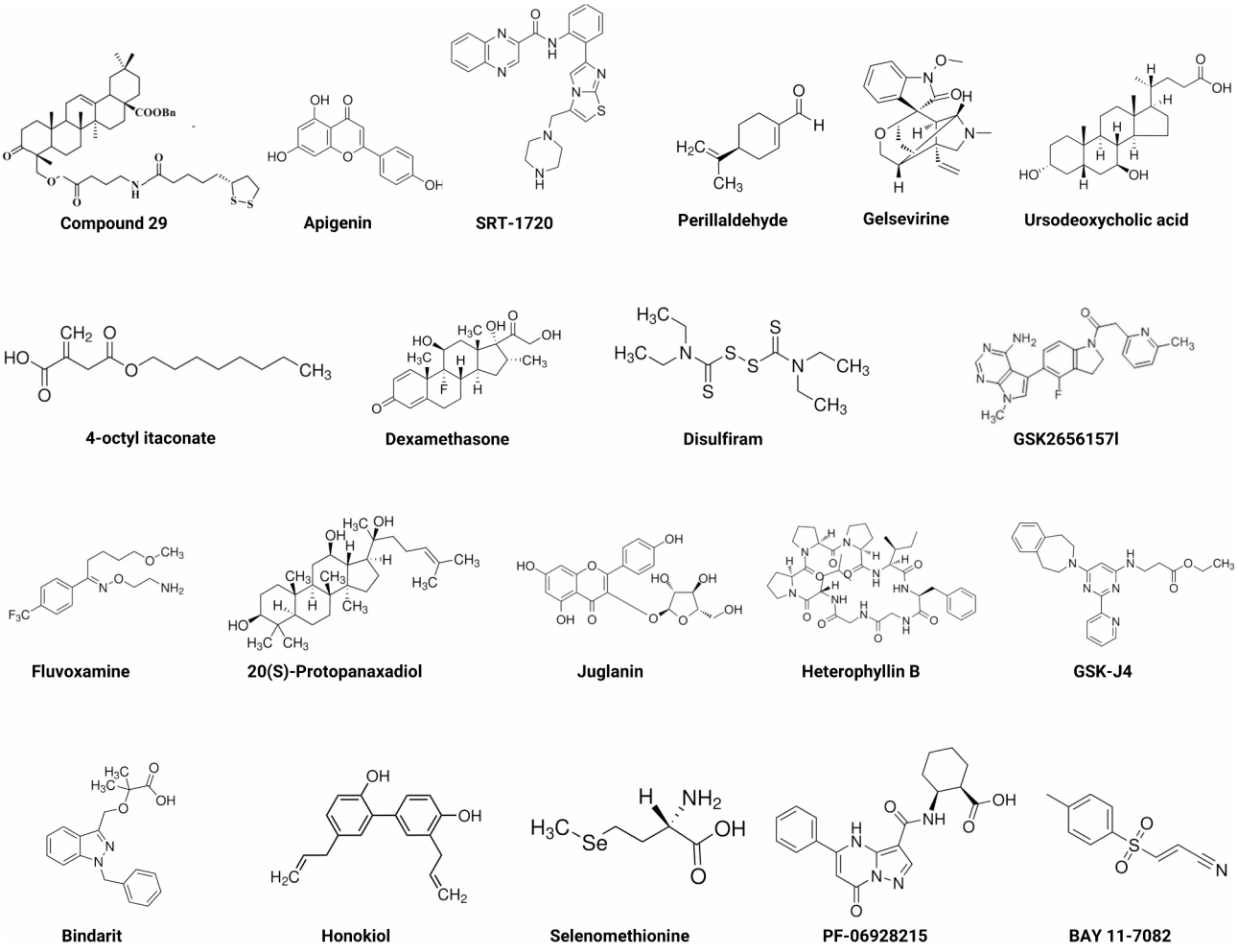

Fig. 6 Chemical structures of small molecules targeting cGAS-STING for lung diseases therapy

signaling pathway [111]. 20(S)-Protopanaxadiol (PPD) increases survival rate. It attenuates pulmonary fibrosis through activating AMPK to inhibit STING expression and TGF-β1/Smad2 signaling pathway in Male C57BL/6 mice treated with bleomycin [113]. QFAE-nB attenuates lung fibrosis through inactivating STING and reducing the signal transduction of TBK1-IRF3 and TBK1-NF-κB [109]. Qingfei xieding prescription reduces mortality, ameliorates lung fibrosis and re-activates autophagy in bleomycin-induced male SD rats [110]. It also restrains mtDNA-cGAS-STING inflammation pathway. Qingfei xieding prescription increases cell viability, decreases LPO and ROS, and mitochondrial damage in TGF-β1-induced lung epithelial MLE-12 cells [110]. It reverses TGF-β-mediated inhibition of autophagy. The protective effects of Qingfei xieding prescription was reversed by autophagy inhibitor in vitro and in vivo. It inhibits mtDNA-cGAS-STING and inflammatory signaling, which were abolished by chloroquine-mediated autophagy inhibition [110]. Together, these results suggest Qingfei xieding prescription attenuates bleomycin-induced pulmonary fibrosis through inhibiting mtDNA-cGAS-STING-induced inflammation and activating autophagy [110]. GSK2656157 (iPERK-2) inhibits the activation of PERK-eIF2α signalling and attenuates pulmonary fibrosis, as evidenced by the preservation of alveolar structures, decreased expression of collagens and fibrosis scores [64].

Lung inflammation

Inhibition of the STING by C-176 attenuates obesity-induced lung inflammation [82]. STING inhibitor C-176 alleviates pathological changes and downregulates expressions of STING and decreases the levels of mRNA and pro-inflammatory cytokines in lung tissues in a high-fat diet (HFD)-induced obese mouse. C-176 suppresses the levels ofTNF-α, IL-6 and IFNβ in BALF [82].

Pulmonary arterial hypertension

STING inhibitors, such as C-176, alleviate the Su/Hy-induced increase in pulmonary artery pressure and

restrain the activation of the NLRP3 inflammasome and proinflammatory cytokines [75].

Radiation-Induced Lung Injury

Pulmozyme, an old drug to treat cystic fibrosis, mitigates RILI through degrading extracellular dsDNA, thereby inactivating cGAS-STING-NLRP3 signaling pathway [72]. The CCL2 inhibitor Bindarit alleviats RILI through decreasing the recruitment and polarization of macrophages [73].

COPD

STING inhibitor H-151 combined dexamethasone augments steroid responsiveness through upregulating HDAC2 and attenuates remodeling in steroid-resistant COPD fibroblasts [67].

Pancreatitis-Associated Lung Injury

Inhibition of JMJD3 by GSK-J4 attenuates lung pathological lesions and decreases the percentage of TNF-a1CD451CD11b1Ly6C1 inflammatory monocytes in the lung, and peripheral blood [70]. C-176 alleviates lung injury and inflammation through adjusting macrophage polarization and inhibiting apoptosis in caerulein and LPS-induced murine model.

AAPV

Pharmacologically inhibiting IFNAR-1, STING, or JAK1/2 decreases disease severity and facilitates recovery [84]. H151 inhibits vasculitis-associated weight loss and reduces the incidence of pulmonary hemorrhages. H151 decreases leukocyte infiltration in the BAL [84]. Baricitnib targets JAK1 downstream of IFNAR-I and is used to treat patients with interferonopathies to reduce weight loss and lung histopathology. Baricitinib decreases degree of developing hemorrhages [84].

Conclusions and perspectives

Emerging evidence indicates that cGAS-STING pathway activation plays a crucial role in the pathogenesis of various lung diseases. Emerging studies have demonstrated that pharmacological inhibition of the cGAS-STING pathway offers many novel therapeutic opportunities to treat lung diseases. Many bioactive compounds exert potential therapeutic effects by inactivating the cGAS-STING pathway, thus offering promising strategies for lung disease management. In this review, we first outline the principal core mechanisms of activation for cGAS-STING signaling, then summarize recent research mechanistically connecting cGAS-STING signaling to the pathogenesis of different lung diseases. Finally, we highlighted several bioactive compounds serving as potential pharmacological antagonists of the cGAS-STING pathway, delineating their beneficial effects in addressing the phenotypes of lung diseases. This review emphasizes the novel potential of cGAS-STING antagonists as novel therapeutic agents for lung diseases.

Interest in cGAS-STING has grown exponentially in the past decade, generating substantial evidence that cGAS-STING signaling plays a pivotal role in a wide range of diseases, including lung diseases. However, many questions remain to be addressed. First, further research is needed to uncover the molecular mechanisms underlying activation of cGAS-STING and its downstream signaling pathway in different types of lung diseases. Second, exploring the interplay between cGAS-STING activation and various regulated cell death (RCD) pathways—such as ferroptosis, autophagy, and pyroptosis—could provide valuable insights into their contribution to lung disease pathogenesis. These interplay must be studied on a disease-specific basis. Third, we have uncovered the molecular threats that activate the cGAS-STING axis in specific lung diseases. However, the signaling pathway and cellular relay through which cGAS-STING triggers these diseases remain poorly understood. Fourth, cGAS-STING signaling is tightly regulated at the level of transcriptional regulation, post-translational modifications, and epigenetic modifications in various diseases, including lung diseases. However, the mechanistic understanding of how cGAS-STING is modulated by these regulatory changes needs to be uncovered in lung diseases. Five, the role of cGAS-STING pathway is dependant of diseases, and makes the cGAS-STING pathway as a double-edged sword. Lastly, it is essential to uncover which genes and proteins regulate cGAS-STING in lung diseases. Identifying the diverse regulators of ferroptosis in different lung diseases remains a challenge to be resolved. These could identify additional nodes of pharmacological intervention.

In summary, despite these considerations, emerging evidence strongly suggests that cGAS-STING pathway inhibition is a significant new direction for treating lung diseases. Direct research on cGAS-STING aligned towards diseases pathogenesis is still needed, but pharmacological antagonism of cGAS-STING may be a promising therapeutic approach for lung diseases.

Acknowledgements

No applicable.

Author contributions

YW and HW designed and conceived the Review. WW and YZ contributed substantially to discussion of the content. LS and HW wrote the manuscript. XZ and HW generated the figures. JSF edited the manuscript. All authors contributed to reviewing and/or editing of manuscript. All authors approved the final manuscript.

Funding

This work was supported in part by the Science Foundation of AMHT (2024YK05).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
Not applicable.

Consent for publication
All of the authors are aware of and agree to the content of the paper and their being listed as a co-author of the paper.

Competing interests
The authors declare no competing interests.

Received: 24 November 2024 / Accepted: 27 January 2025
Published online: 07 February 2025

References

1. Skopelja-Gardner S, An J, Elkon KB. Role of the cGAS-STING pathway in systemic and organ-specific diseases. Nat Rev Nephrol. 2022;18:558–72.
2. Zhang Z, Zhou H, Ouyang X, Dong Y, Sarapultsev A, Luo S, et al. Multifaceted functions of STING in human health and disease: from molecular mechanism to targeted strategy. Signal Transduct Target Ther. 2022;7:394.
3. Motwani M, Pesiridis S, Fitzgerald KA. DNA sensing by the cGAS-STING pathway in health and disease. Nat Rev Genet. 2019;20:657–74.
4. Yang K, Tang Z, Xing C, Yan N. STING signaling in the brain: molecular threats, signaling activities, and therapeutic challenges. Neuron; 2023. S0896-6273(23)00795-00795X [pii].
5. Ferecskó AS, Smallwood MJ, Moore A, Liddle C, Newcombe J, Holley J, et al. STING-Triggered CNS inflammation in human neurodegenerative diseases. Biomedicines. 2023;11:1375.
6. Fryer AL, Abdullah A, Taylor JM, Crack PJ. The complexity of the cGAS-STING pathway in CNS pathologies. Front Neurosci. 2021;15:621501.
7. Huang Y, Liu B, Sinha SC, Amin S, Gan L. Mechanism and therapeutic potential of targeting cGAS-STING signaling in neurological disorders. Mol Neurodegener. 2023;18:79.
8. Paul BD, Snyder SH, Bohr VA. Signaling by cGAS-STING in Neurodegeneration, Neuroinflammation, and aging. Trends Neurosci. 2021;44:83–96.
9. Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. Nat Rev Immunol. 2021;21:548–69.
10. Sheridan C. Drug developers switch gears to inhibit STING. Nat Biotechnol. 2019;37:199–201.
11. ISAACS A. Interferon Sci Am 1961;204:51–7.
12. Dvorkin S, Cambier S, Volkman HE, Stetson DB. New frontiers in the cGAS-STING intracellular DNA-sensing pathway. Immunity. 2024;57:718–30.
13. ISAACS A, LINDENMANN J. Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci. 1957;147:258–67.
14. ISAACS A, LINDENMANN J, VALENTINE RC. Virus interference. II. Some properties of interferon. Proc R Soc Lond B Biol Sci. 1957;147:268–73.
15. Stark GR, Kerr IM, Williams BR, Silverman RH, Schreiber RD. How cells respond to interferons. Annu Rev Biochem. 1998;67:227–64.
16. Sen R, Baltimore D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. Cell. 1986;46:705–16.
17. Fujita T, Sakakibara J, Sudo Y, Miyamoto M, Kimura Y, Taniguchi T. Evidence for a nuclear factor(s), IRF-1, mediating induction and silencing properties to human IFN-beta gene regulatory elements. EMBO J. 1988;7:3397–405.
18. Yoneyama M, Suhara W, Fukuhara Y, Fukuda M, Nishida E, Fujita T. Direct triggering of the type I interferon system by virus infection: activation of a transcription factor complex containing IRF-3 and CBP/p300. EMBO J. 1998;17:1087–95.
19. Pomerantz JL, Baltimore D. NF-kappaB activation by a signaling complex containing TRAF2, TANK and TBK1, a novel IKK-related kinase. EMBO J. 1999;18:6694–704.
20. Yoneyama M, Kikuchi M, Natsukawa T, Shinobu N, Imaizumi T, Miyagishi M, et al. The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat Immunol. 2004;5:730–7.
21. Yoneyama M, Kikuchi M, Matsumoto K, Imaizumi T, Miyagishi M, Taira K, et al. Shared and unique functions of the DExD/H-box helicases RIG-I, MDA5, and LGP2 in antiviral innate immunity. J Immunol. 2005;175:2851–8.
22. Kawai T, Takahashi K, Sato S, Coban C, Kumar H, Kato H, et al. IPS-1, an adaptor triggering RIG-I- and Mda5-mediated type I interferon induction. Nat Immunol. 2005;6:981–8.
23. Meylan E, Curran J, Hofmann K, Moradpour D, Binder M, Bartenschlager R, et al. Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. Nature. 2005;437:1167–72.
24. Seth RB, Sun L, Ea CK, Chen ZJ. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-kappaB and IRF 3. Cell. 2005;122:669–82.
25. Xu LG, Wang YY, Han KJ, Li LY, Zhai Z, Shu HB. VISA is an adapter protein required for virus-triggered IFN-beta signaling. Mol Cell. 2005;19:727–40.
26. Kato H, Takahasi K, Fujita T. RIG-I-like receptors: cytoplasmic sensors for non-self RNA. Immunol Rev. 2011;243:91–8.
27. Ishii KJ, Coban C, Kato H, Takahashi K, Torii Y, Takeshita F, et al. A toll-like receptor-independent antiviral response induced by double-stranded B-form DNA. Nat Immunol. 2006;7:40–8.
28. Stetson DB, Medzhitov R. Recognition of cytosolic DNA activates an IRF3-dependent innate immune response. Immunity. 2006;24:93–103.
29. Zhong B, Yang Y, Li S, Wang YY, Li Y, Diao F, et al. The adaptor protein MITA links virus-sensing receptors to IRF3 transcription factor activation. Immunity. 2008;29:538–50.
30. Ishikawa H, Barber GN. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature. 2008;455:674–8.
31. Jin L, Waterman PM, Jonscher KR, Short CM, Reisdorph NA, Cambier JC. MPYS, a novel membrane tetraspanner, is associated with major histocompatibility complex class II and mediates transduction of apoptotic signals. Mol Cell Biol. 2008;28:5014–26.
32. Sun W, Li Y, Chen L, Chen H, You F, Zhou X, et al. ERIS, an endoplasmic reticulum IFN stimulator, activates innate immune signaling through dimerization. Proc Natl Acad Sci U S A. 2009;106:8653–8.
33. Ishikawa H, Ma Z, Barber GN. STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity. Nature. 2009;461:788–92.
34. Abe T, Harashima A, Xia T, Konno H, Konno K, Morales A, et al. STING recognition of cytoplasmic DNA instigates cellular defense. Mol Cell. 2013;50:5–15.
35. Burdette DL, Monroe KM, Sotelo-Troha K, Iwig JS, Eckert B, Hyodo M, et al. STING is a direct innate immune sensor of cyclic di-GMP. Nature. 2011;478:515–8.
36. Sun L, Wu J, Du F, Chen X, Chen ZJ. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science. 2013;339:786–91.
37. Wu J, Sun L, Chen X, Du F, Shi H, Chen C, et al. Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. Science. 2013;339:826–30.
38. Hopfner KP, Hornung V. Molecular mechanisms and cellular functions of cGAS-STING signalling. Nat Rev Mol Cell Biol. 2020;21:501–21.
39. Gall A, Treuting P, Elkon KB, Loo YM, Gale M, Jr, Barber GN, et al. Autoimmunity initiates in nonhematopoietic cells and progresses via lymphocytes in an interferon-dependent autoimmune disease. Immunity. 2012;36:120–31.
40. Jin L, Getahun A, Knowles HM, Mogan J, Akerlund LJ, Packard TA, et al. STING/MPYS mediates host defense against Listeria monocytogenes infection by regulating Ly6C(hi) monocyte migration. J Immunol. 2013;190:2835–43.
41. Civril F, Deimling T, de Oliveira Mann CC, Ablasser A, Moldt M, Witte G, et al. Structural mechanism of cytosolic DNA sensing by cGAS. Nature. 2013;498:332–7.
42. Gao P, Ascano M, Wu Y, Barchet W, Gaffney BL, Zillinger T, et al. Cyclic [G(2',5') pA(3',5')p] is the metazoan second messenger produced by DNA-activated cyclic GMP-AMP synthase. Cell. 2013;153:1094–107.
43. Kranzusch PJ, Lee AS, Berger JM, Doudna JA. Structure of human cGAS reveals a conserved family of second-messenger enzymes in innate immunity. Cell Rep. 2013;3:1362–8.
44. Li X, Shu C, Yi G, Chaton CT, Shelton CL, Diao J, et al. Cyclic GMP-AMP synthase is activated by double-stranded DNA-induced oligomerization. Immunity. 2013;39:1019–31.
45. Zhang X, Shi H, Wu J, Zhang X, Sun L, Chen C, et al. Cyclic GMP-AMP containing mixed phosphodiester linkages is an endogenous high-affinity ligand for STING. Mol Cell. 2013;51:226–35.
46. Shang G, Zhang C, Chen ZJ, Bai XC, Zhang X. Cryo-EM structures of STING reveal its mechanism of activation by cyclic GMP-AMP. Nature. 2019;567:389–93.

47. Shu C, Yi G, Watts T, Kao CC, Li P. Structure of STING bound to cyclic di-GMP reveals the mechanism of cyclic dinucleotide recognition by the immune system. Nat Struct Mol Biol. 2012;19:722–4.
48. Comish PB, Liu MM, Huebinger R, Carlson D, Kang R, Tang D. The cGAS-STING pathway connects mitochondrial damage to inflammation in burn-induced acute lung injury in rat. Burns. 2022;48:168–75.
49. Chen K, Cagliani J, Aziz M, Tan C, Brenner M. Wang,Extracellular CIRP activates STING to exacerbate hemorrhagic shock. JCI Insight. 2021;6:e143715.
50. Wang N, Wang X, Li Y, Shen H, Liu Z, Ma Z, Li Q, Zhao M. The STING-IRF3 pathway contributes to paraquat-induced acute lung injury. Toxicol Mech Methods. 2022;32:145–57.
51. Zhao C, Liang F, Ye M, et al. GSDMD promotes neutrophil extracellular traps via mtDNA-cGAS-STING pathway during lung ischemia/reperfusion. Cell Death Discov. 2023;9(1):368.
52. Liu L, Mao Y, Xu B, et al. Induction of neutrophil extracellular traps during tissue injury: involvement of STING and toll-like receptor 9 pathways. Cell Prolif. 2020;53(10):e12775.
53. Joshi JC, Joshi B, Rochford I, Rayees S, Akhter MZ, Baweja S, Chava KR, Tauseef M, Abdelkarim H, Natarajan V, Gaponenko V. Mehta,SPHK2-Generated S1P in CD11b(+) macrophages blocks STING to suppress the inflammatory function of alveolar macrophages. Cell Rep. 2020;30:4096–e41095.
54. Joshi JC, Joshi B, Rochford I, Mehta D., S1P generation by Sphingosine Kinase-2 in recruited macrophages resolves lung inflammation by blocking STING Signaling in Alveolar macrophages. J Cell Signal. 2021;2:47–51.
55. Ning L, Wei W, Wenyang J, Rui X, Qing G. Cytosolic DNA-STING-NLRP3 axis is involved in murine acute lung injury induced by lipopolysaccharide. Clin Transl Med. 2020;10:e228.
56. Zhang H, Chen Z, Zhou J, Gu J, Wu H, Jiang Y, Gao S, Liao Y, Shen R, Miao C. Chen,NAT10 regulates neutrophil pyroptosis in sepsis via acetylating ULK1 RNA and activating STING pathway. Commun Biol. 2022;5:916.
57. Li R, Zhao Y, Zhang X, Yang L. Zou,NLRC3 participates in inhibiting the pulmonary inflammatory response of Sepsis-Induced Acute Lung Injury. Immunol Invest. 2023;52:567–82.
58. Li N, Liu B, He R, Li G, Xiong R, Fu T, Li D, Xu C, Wang B. Geng,HDAC3 promotes macrophage pyroptosis via regulating histone deacetylation in acute lung injury. iScience. 2023;26:107158.
59. Jiang T, Liu E, Li Z et al. SIRT1-Rab7 axis attenuates NLRP3 and STING activation through late endosomal-dependent mitophagy during sepsis-induced acute lung injury. Int J Surg. 2024.
60. Yu W, Yang M, Lv B, Yu Y, Zhu W. CD40L-Activated DC promotes Th17 differentiation and inhibits Th2 differentiation in Sepsis-Induced Lung Injury via cGAS-STING signaling. Biochem Genet 2024.
61. Liu Q, Wu J, Zhang X, Li X, Wu X, Zhao Y. Ren,circulating mitochondrial DNA-triggered autophagy dysfunction via STING underlies sepsis-related acute lung injury. Cell Death Dis. 2021;12:673.
62. Zhu S, Yu Y, Qu M, Qiu Z, Zhang H, Miao C, et al. Neutrophil extracellular traps contribute to immunothrombosis formation via the STING pathway in sepsis-associated lung injury. Cell Death Discov. 2023;9(1):315.
63. Zhao J, Zhen N, Zhou Q, et al. NETs promote Inflammatory Injury by activating cGAS-STING pathway in Acute Lung Injury. Int J Mol Sci. 2023;24(6):5125.
64. Zhang D, Liu Y, Zhu Y, et al. A non-canonical cGAS-STING-PERK pathway facilitates the translational program critical for senescence and organ fibrosis. Nat Cell Biol. 2022;24(5):766–82.
65. Wu X, Jiang Y, Li R, Xia Y, Li F, Zhao M, Li G. Tan,Ficolin B secreted by alveolar macrophage exosomes exacerbates bleomycin-induced lung injury via ferroptosis through the cGAS-STING signaling pathway. Cell Death Dis. 2023;14:577.
66. Liu J, Xu F, Guo M, Gao D, Song Y. Nasal instillation of polystyrene nanoplastics induce lung injury via mitochondrial DNA release and activation of the cyclic GMP-AMP synthase-stimulator of interferon genes-signaling cascade. Sci Total Environ 2024:174674.
67. Mdkhana B, Saheb Sharif-Askari N, Ramakrishnan RK, et al. Nucleic acid sensor STING drives remodeling and its inhibition enhances steroid responsiveness in chronic obstructive pulmonary disease. PLoS ONE. 2023;18(7):e0284061.
68. Lu C, Zhang X, Ma C, et al. Nontypeable Haemophilus influenzae DNA stimulates type I interferon expression via STING signaling pathway. Biochim Biophys Acta Mol Cell Res. 2018;1865(4):665–73.
69. Nascimento M, Gombault A, Lacerda-Queiroz N, et al. Self-DNA release and STING-dependent sensing drives inflammation to cigarette smoke in mice. Sci Rep. 2019;9(1):14848.
70. Chen L, Zhang X, Liu Y, Liu L, Liang X, Yang S, Xia Q, Jin T, Ma Y, Chen Y, Yuan X, Tie Y, Gu Y, Fang C, Chen S, Mo F, Yu T, Hu Y, Qian Z, Peng Y, Geng J, Zhou Z, Wu M, Ding J, Yang D, Wei X. JMJD3 is required for Acute Pancreatitis and Pancreatitis-Associated Lung Injury. J Immunol (Baltimore Md: 1950). 2023;210:180–90.
71. Peng Y, Li Y, Yang Y, Shi T, Liu R, Luan Y. Yin,the role and potential Regulatory mechanism of STING modulated macrophage apoptosis and differentiation in severe Acute Pancreatitis-Associated Lung Injury. J Interferon Cytokine Res. 2023;43:455–68.
72. Zhang Y, Li Z, Hong W, Hsu S, Wang B, Zeng Z, Du S. STING-Dependent sensing of Self-DNA driving pyroptosis contributes to Radiation-Induced Lung Injury. Int J Radiat Oncol Biol Phys. 2023;117:928–41.
73. Ni J, Guo T, Zhou Y, Jiang S, Zhang L, Zhu Z. STING signaling activation modulates macrophage polarization via CCL2 in radiation-induced lung injury. J Transl Med. 2023;21:590.
74. Tang Y, Wang T, Gu L et al. USP11 exacerbates Radiation-Induced Pneumonitis by activating endothelial cell inflammatory response via OTUD5-STING signaling. Int J Radiat Oncol Biol Phys. 2024: S0360-3016(24)00307-9 [pii].
75. Wu DD, Deng Y, Liao J, Xie SS, Meng H, Lan WF. STING mediates SU5416/hypoxia-induced pulmonary arterial hypertension in rats by regulating macrophage NLRP3 inflammasome activation. Immunobiology. 2023;228(2):152345.
76. Pham AT, Oliveira AC, Albanna M, et al. Non-interferon-dependent role of STING Signaling in Pulmonary Hypertension. Arterioscler Thromb Vasc Biol. 2024;44(1):124–42.
77. Deng L, Cao C, Cai Z, Wang Z, Leng B, Chen Z et al. STING contributes to pulmonary hypertension by targeting the Interferon and BMPR2 Signaling through regulating F2RL3. Am J Respir Cell Mol Biol 2024.
78. Benmerzoug S, Rose S, Bounab B, et al. STING-dependent sensing of self-DNA drives silica-induced lung inflammation. Nat Commun. 2018;9(1):5226.
79. Gao Y, Xu W, Dou X, et al. Mitochondrial DNA leakage caused by Streptococcus pneumoniae Hydrogen Peroxide promotes type I IFN expression in lung cells. Front Microbiol. 2019;10:630.
80. Patel S, Tucker HR, Gogoi H, Mansouri S, Jin L. cGAS-STING and MyD88 pathways synergize in Ly6C(hi) monocyte to promote Streptococcus pneumoniae-Induced Late-Stage Lung IFNγ production. Front Immunol. 2021;12:699702.
81. Papinska J, Bagavant H, Gmyrek GB, Deshmukh US. Pulmonary involvement in a mouse model of Sjögren's Syndrome Induced by STING activation. Int J Mol Sci. 2020;21(12):4512.
82. Qi Y, Wu Z, Chen D, Zhu L, Yang Y. A role of STING signaling in obesity-induced lung inflammation. Int J Obes (Lond). 2023;47(4):325–34.
83. Ozasa K, Temizoz B, Kusakabe T, et al. Cyclic GMP-AMP triggers Asthma in an IL-33-Dependent manner that is blocked by Amlexanox, a TBK1 inhibitor. Front Immunol. 2019;10:2212.
84. Kessler N, Viehmann SF, Krollmann C, et al. Monocyte-derived macrophages aggravate pulmonary vasculitis via cGAS/STING/IFN-mediated nucleic acid sensing. J Exp Med. 2022;219(10):e20220759.
85. Liu Y, Jesus AA, Marrero B, et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med. 2014;371(6):507–18.
86. Warner JD, Irizarry-Caro RA, Bennion BG, et al. STING-associated vasculopathy develops independently of IRF3 in mice. J Exp Med. 2017;214(11):3279–92.
87. Luksch H, Stinson WA, Platt DJ, et al. STING-associated lung disease in mice relies on T cells but not type I interferon. J Allergy Clin Immunol. 2019;144(1):254–e2668.
88. Siedel H, Roers A, Rösen-Wolff A, Luksch H. Type I interferon-independent T cell impairment in a Tmem173 N153S/WT mouse model of STING associated vasculopathy with onset in infancy (SAVI). Clin Immunol. 2020;216:108466.
89. Saldanha RG, Balka KR, Davidson S, et al. A mutation outside the Dimerization Domain Causing Atypical STING-Associated Vasculopathy with Onset in Infancy. Front Immunol. 2018;9:1535.
90. Melki I, Rose Y, Uggenti C, et al. Disease-associated mutations identify a novel region in human STING necessary for the control of type I interferon signaling. J Allergy Clin Immunol. 2017;140(2):543–e5525.
91. Ou L, Zhang P, Huang Z, et al. Targeting STING-mediated pro-inflammatory and pro-fibrotic effects of alveolar macrophages and fibroblasts blunts silicosis caused by silica particles. J Hazard Mater. 2023;458:131907.
92. Chen M, Lei S, Zhou Z, Wang M, Feng C, Gao X, et al. Design, synthesis, and pharmacological evaluation of Spiro[carbazole-3,3'-pyrrolidine] derivatives as cGAS inhibitors for treatment of Acute Lung Injury. J Med Chem. 2024;67:6268–91.
93. Myakala K, Jones BA, Wang XX, Levi M. Sacubitril/valsartan treatment has differential effects in modulating diabetic kidney disease in db/db mice and

KKAy mice compared with valsartan treatment. Am J Physiol Ren Physiol. 2021;320(6):F1133–51.
94. Li H, Xie W, Gao X, Geng Z, Gao J, Ma G, Liu X, Han S, Chen Y, Wen X, Bi Y. Zhang,Design and synthesis of novel hederagonic acid analogs as potent anti-inflammatory compounds capable of protecting against LPS-induced acute lung injury. Eur J Med Chem. 2024;263:115941.
95. Zhou XW, Wang J, Tan WF. Apigenin suppresses Innate Immune responses and ameliorates Lipopolysaccharide-Induced inflammation via inhibition of STING/IRF3 pathway. Am J Chin Med. 2024: 1–22.
96. Wei J, Liu Z, Sun H, Xu L. Perillaldehyde ameliorates lipopolysaccharide-induced acute lung injury via suppressing the cGAS/STING signaling pathway. Int Immunopharmacol. 2024;130:111641.
97. He YQ, Zhou CC, Deng JL, Wang L. Chen,Tanreqing inhibits LPS-Induced Acute Lung Injury in vivo and in Vitro through Downregulating STING Signaling Pathway. Front Pharmacol. 2021;12:746964.
98. Wen J, Qin S, Li Y, Zhang P, Zhan X, Fang M, Shi C, Mu W, Kan W, Zhao J, Hui S, Hou M, Li H, Xiao X, Xu G. Bai,flavonoids derived from licorice suppress LPS-induced acute lung injury in mice by inhibiting the cGAS-STING signaling pathway. Food Chem Toxicol. 2023;175:113732.
99. Zeng L, et al. ALK is a therapeutic target for lethal sepsis. Sci Transl Med. 2017;9:eaan5689.
100. Ge W, et al. LDK378 improves micro- and macro-circulation via alleviating STING-mediated inflammatory injury in a Sepsis rat model induced by Cecal ligation and puncture. J Inflamm (London England). 2019;16:3.
101. Chen Y, Bian H, Lv J, et al. Gelsevirine is a novel STING-specific inhibitor and mitigates STING-related inflammation in sepsis. Front Immunol. 2023;14:1190707.
102. He YQ, Deng JL, Zhou CC, et al. Ursodeoxycholic acid alleviates sepsis-induced lung injury by blocking PANoptosis via STING pathway. Int Immunopharmacol. 2023;125Pt B:111161.
103. Zhang SY, Xu QP, Shi LN, et al. Soluble CD4 effectively prevents excessive TLR activation of resident macrophages in the onset of sepsis. Signal Transduct Target Ther. 2023;8(1):236.
104. Wu YT, Xu WT, Zheng L, et al. 4-octyl itaconate ameliorates alveolar macrophage pyroptosis against ARDS via rescuing mitochondrial dysfunction and suppressing the cGAS/STING pathway. Int Immunopharmacol. 2023;118:110104.
105. Qi X, Wang J, Fei F, et al. Myricetin-loaded Nanomicelles protect against Cisplatin-Induced Acute kidney Injury by inhibiting the DNA Damage-cGAS-STING signaling pathway. Mol Pharm. 2023;20(1):136–46.
106. Liu S, Gao X, Yin Y, et al. Silk fibroin peptide self-assembled nanofibers delivered naringenin to alleviate cisplatin-induced acute kidney injury by inhibiting mtDNA-cGAS-STING pathway. Food Chem Toxicol. 2023;177:113844.
107. Yang M, Ma YX, Zhi Y, Wang HB, Zhao L, Wang PS. Niu,inhibitors of IFN gene stimulators (STING) improve intestinal ischemia-reperfusion-induced acute lung injury by activating AMPK signaling. Eur J Med Res. 2022;27:79.
108. Huang R, Shi Q, Zhang S, et al. Inhibition of the cGAS-STING pathway attenuates Lung Ischemia/Reperfusion Injury via regulating endoplasmic reticulum stress in alveolar epithelial type II cells of rats. J Inflamm Res. 2022;15:5103–19.
109. Wei X, Jing J, Huang R, et al. QFAE-nB alleviates pulmonary fibrosis by inhibiting the STING pathway in mice. J Ethnopharmacol. 2024;319(Pt 2):117295.
110. Wang Y, He X, Wang H, Hu W, Sun L. Qingfei xieding prescription ameliorates mitochondrial DNA-initiated inflammation in bleomycin-induced pulmonary fibrosis through activating autophagy. J Ethnopharmacol. 2024;325:117820.
111. Deng J, He Y, Sun G, et al. Tanreqing injection protects against bleomycin-induced pulmonary fibrosis via inhibiting STING-mediated endoplasmic reticulum stress signaling pathway. J Ethnopharmacol. 2023;305:116071.
112. Xie X, Wu X, Zhao D, et al. Fluvoxamine alleviates bleomycin-induced lung fibrosis via regulating the cGAS-STING pathway. Pharmacol Res. 2023;187:106577.
113. Ren G, Lv W, Ding Y, et al. Ginseng saponin metabolite 20(S)-protopanaxadiol relieves pulmonary fibrosis by multiple-targets signaling pathways. J Ginseng Res. 2023;47(4):543–51.
114. Sun SC, Han R, Hou SS, Yi HQ, Chi SJ. Zhang,Juglanin alleviates bleomycin-induced lung injury by suppressing inflammation and fibrosis via targeting sting signaling. Biomed Pharmacother. 2020;127:110119.
115. Shi W, Hao J, Wu Y, et al. Protective effects of heterophyllin B against bleomycin-induced pulmonary fibrosis in mice via AMPK activation. Eur J Pharmacol. 2022;921:174825.
116. Zhou Q, Yi G, Chang M, Li N, Bai Y, Li H, et al. Activation of Sirtuin3 by honokiol ameliorates alveolar epithelial cell senescence in experimental silicosis via the cGAS-STING pathway. Redox Biol. 2024;74:103224.
117. Feng Z, Liao X, Peng J, et al. PCSK9 causes inflammation and cGAS/STING pathway activation in diabetic nephropathy. FASEB J. 2023;37(9):e23127.
118. Wang X, et al. Selenium supplementation protects against Lipopolysaccharide-Induced Heart Injury via Sting Pathway in mice. Biol Trace Elem Res. 2021;199:1885–92.
119. Wu Y, Wang Z, Du Q, Zhu Z, Chen T, Xue Y, Wang Y, Zeng Q, Shen C, Jiang C, Liu L, Zhu H. Q. Liu,Pharmacological Effects and Underlying Mechanisms of Licorice-Derived Flavonoids, Evid Based Complement Alternat Med 2022 (2022) 9523071.

Publisher's note