

cGAS–STING signaling pathway as a therapeutic target in human diseases

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Abstract

The cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)–stimulator of interferon genes (STING) signaling pathway has been extensively documented since its discovery in 2013. The cGAS–STING signaling pathway is activated upon cytoplasmic DNA stimulation and triggers innate immunity. The cGAS–STING signaling pathway is pivotal in antiviral defense and tumor immunity and significantly influences various pathological conditions. Currently, the cGAS–STING signaling pathway has been explored as a potential target for several diseases. Here, we aim to summarize the mechanisms of cGAS–STING signaling pathway activation, signal transduction, and regulation. We review the role of cGAS–STING in pathological conditions across multiple human systems. We also summarize recent progress in the development of drugs targeting this signaling pathway and ongoing clinical trials. This review may deepen our understanding of the cGAS–STING signaling pathway and unlock its translational potential for human diseases.

Keywords: cGAS–STING; Pathogenesis; Human disease spectrum; Agonist; Inhibitor; Clinical trials

Introduction

The innate immune system serves as the first line of defense for mammals and plays a crucial role in the host's defense against pathogens. The innate immune system detects various pathogens and damage-related molecular patterns through pattern recognition receptors.^[1] Pattern recognition receptors can promote the production of type I interferons (IFN-Is) by inducing the expression of interferon-stimulated genes, thereby enhancing autonomous cellular defense mechanisms and activating the adaptive immune system. The cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)–stimulator of interferon genes (STING) signaling pathway is a component of the innate immune system that functions to detect the presence of cytosolic DNA and triggers the expression of inflammatory genes.^[2] Under normal conditions, DNA is typically confined within the nucleus or other organelles, such as mitochondria.^[3] However, cells are damaged when the host is in an abnormal state, such as during tumorigenesis, viral infection, or bacterial invasion, and then the DNA spreads into the cytoplasm.^[3] Cytosolic DNA then triggers the cGAS–STING signaling pathway and induces an immune response. Unlike other innate immune signaling mechanisms, the cGAS–STING signaling pathway is triggered by DNA and lacks any pathogen-specific attributes.^[4] cGAS

can recognize a wide range of exogenous and self-derived DNA species.^[5,6] Accumulating evidence suggests that dysregulation of this highly versatile innate immune-sensing system can disrupt cellular and biological homeostasis by stimulating abnormal innate immune responses associated with many pathologies.^[7–9] However, the mechanism that determines the protective and pathogenic activity of cGAS–STING in the host body is still controversial, and it seems to depend on the intensity and chronicity of cGAS–STING signaling.

The role of the cGAS–STING signaling pathway in various diseases has been extensively studied since the discovery of cGAS–STING in 2013. We conducted a bibliometric analysis of the cGAS–STING signaling pathway. The data revealed a dramatic increase in the number of publications related to this pathway in recent years [Figure 1A]. The research focus has expanded from initial investigations into cytosolic DNA sensors and innate immunity to current emphases on blockade and structural basis [Figure 1B and C]. Research in this field is broadly distributed across disciplines, including immunology, molecular biology, cell biology, oncology, and pharmacology [Figure 1D]. However, there is a lack of systematic reviews of the cGAS–STING signaling pathway in the human disease spectrum. Therefore, we selected literature

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000003904

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Chinese Medical Journal 2025;138(24)

Received: 11-04-2025; Online: 21-11-2025 Edited by: Yuanyuan Ji

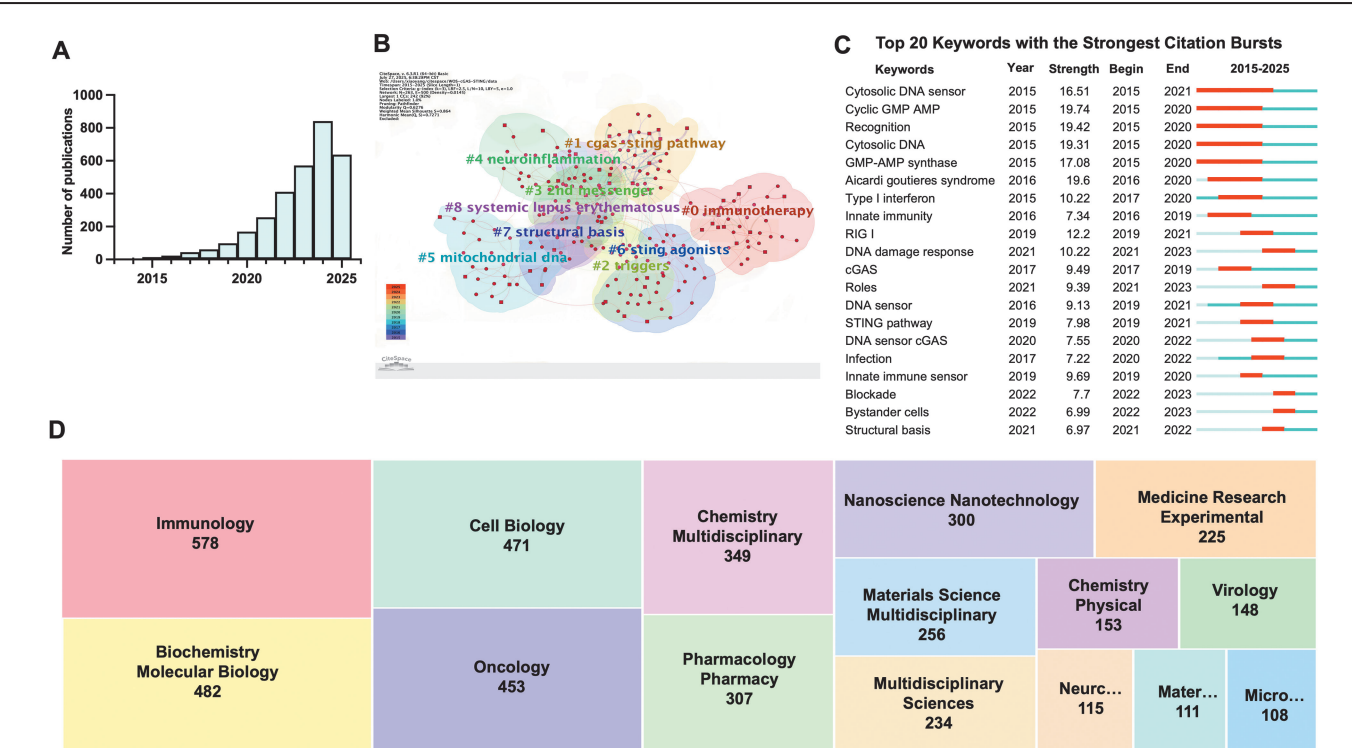


Figure 1: Bibliometric analysis of the cGAS–STING signaling pathway. (A–D) A bibliometric analysis of the cGAS–STING signaling pathway was performed via CiteSpace software and the WOS database. The analysis primarily included (A) publication volume, (B) keyword co-occurrence clustering analysis, (C) keyword burst detection clustering analysis (The light blue represents the range from 2015 to 2025, the blue indicates the duration of keyword appearance, and the red shows the duration of keyword bursts), and (D) research hotspot domain analysis. cGAS: Cyclic GMP-AMP synthase; STING: Stimulator of interferon genes; WOS: Web of Science.

published between 2016 and 2025, with a predominant focus (70%) on studies from the most recent five-year period (2021–2025) for this review. Studies published in non-English journals were excluded. This review briefly introduces the molecular mechanism of the cGAS–STING signaling pathway and systematically summarizes the research status of the cGAS–STING signaling pathway in the human disease spectrum. We also review current clinical trials related to the cGAS–STING signaling pathway and discuss the potential of cGAS–STING in the clinical treatment of various systemic diseases.

Molecular Mechanism of the cGAS–STING Signaling Pathway

Activation of cGAS by double-stranded DNA (dsDNA)

The activation of cGAS by dsDNA plays a pivotal role in the immune response to both invading pathogens and self-damaged DNA [Figure 2]. As a member of the cGAS/DncV-like nucleotidyltransferase family, cGAS is an evolutionarily conserved protein that synthesizes cyclic oligonucleotide second messengers in response to aberrant DNA.^[10] Structurally, cGAS consists of an N-terminal positively charged domain responsible for stabilizing cGAS dimers and a globular C-terminal catalytic domain, which includes a nucleotidyltransferase core for enzymatic activity and a mab21 domain-containing protein 1 for DNA binding.^[11] Although cGAS is traditionally regarded as a cytoplasmic protein, recent studies have demonstrated that it can also localize to the nucleus and plasma membrane.^[12–14] In human HeLa cells and mouse

embryonic fibroblasts, approximately 70–80% of cGAS is found within the nucleus.^[12] Further investigations are warranted to elucidate the potential structural and functional distinctions among the nuclear, cytoplasmic, and membrane-bound forms of cGAS.

cGAS activation is initiated by both exogenous pathogen-derived DNA and endogenous self-damaged DNA [Figure 2], including mitochondrial DNA (mtDNA) and nuclear DNA.^[15,16] Ribosomal stress can cause the dissociation of cGAS from nucleosomes, thereby facilitating its activation within the cytoplasm^[17] [Figure 2]. cGAS recognizes aberrant DNA in the cytoplasm via its disordered N-terminal region and C-terminal catalytic domain.^[11] However, owing to the relatively weak binding affinities at these sites, endogenous cGAS struggles to form stable interactions. Liquid–liquid phase separation significantly enhances this process by concentrating cGAS and DNA, thereby promoting robust interactions and switch-like activation.^[18] Consequently, DNA-induced oligomerization and phase separation lead to a marked increase in cGAS activation.

cGAS synthesizes cyclic GMP-AMP (cGAMP) upon binding to dsDNA

Upon binding to dsDNA, cGAS catalyzes the synthesis of cGAMP, which serves as a critical intermediary in transmitting signals from cGAS-bound DNA to subsequent STING activation [Figure 2]. The formation of a 2:2 cGAS-DNA complex is essential for the allosteric

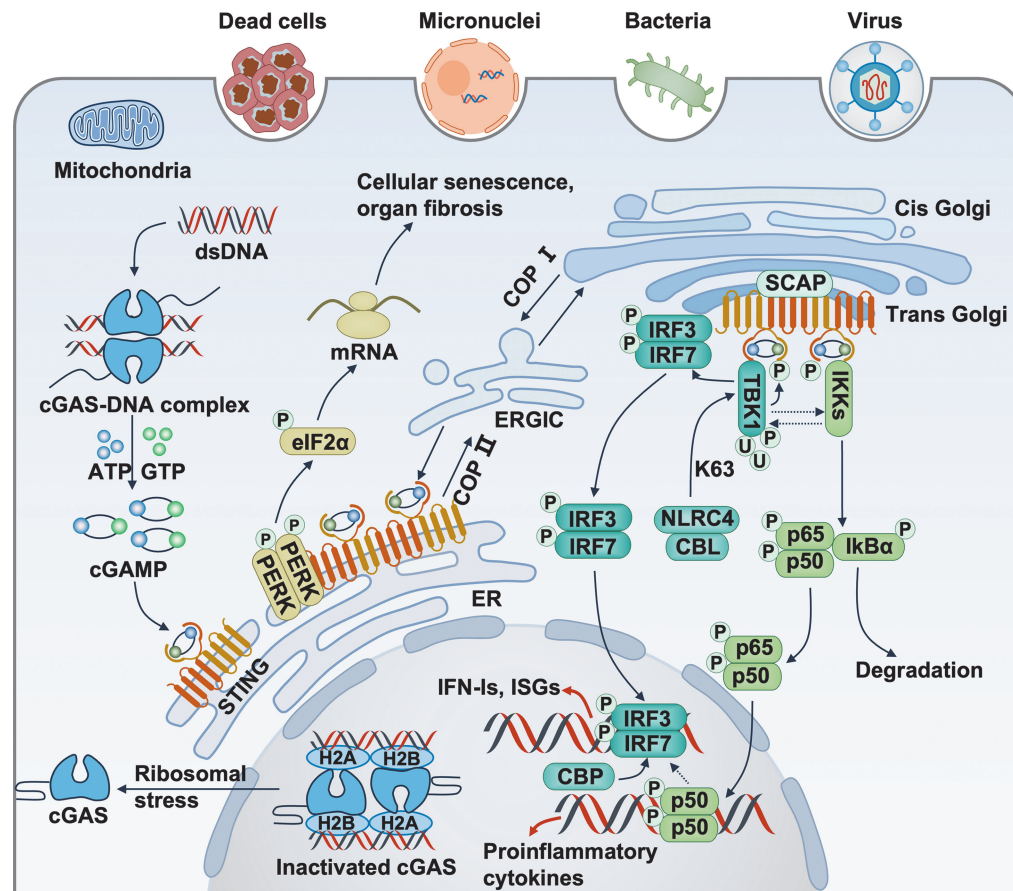


Figure 2: Cytosolic DNA sensing by the cGAS–STING signaling pathway. cGAS is a critical cytosolic DNA sensor that elicits a robust innate immune response by producing cGAMP, which binds to and activates STING in response to DNA from pathogens or hosts. Activated STING leaves the endoplasmic reticulum membrane and enters the Golgi apparatus via the ERGIC, leading to the production of IFN-Is by activating the TBK1–IRF3 signaling pathway. STING can activate NF-κB-dependent proinflammatory cytokine expression. STING can also promote cellular senescence and fibrosis through PERK–eIF2α signaling. ATP: Adenosine triphosphate; CBL: Cbl proto-oncogene; CBP: CREB-binding protein; cGAS: Cyclic GMP–AMP synthase; cGAMP: Cyclic GMP–AMP; COP II: Coatomer protein complex II; dsDNA: Double-stranded DNA; ER: Endoplasmic reticulum; ERGIC: ER–Golgi intermediate compartment; eIF2α: Eukaryotic initiation factor 2α; GTP: Guanosine triphosphate; IFN-Is: Type I interferons; IκBα: Inhibitor of NF-κB; IKKs: IκB kinases; IRF: Interferon regulatory factor; ISGs: Interferon-stimulated genes; NF-κB: Nuclear factor kappa B; NLRC4: NOD-like receptor family CARD domain containing 4; PERK: PKR-like endoplasmic reticulum kinase; SCAP: Sterol regulatory element-binding protein cleavage-activating protein; STING: Stimulator of interferon genes; TBK1: Tank binding kinase 1. Created with PowerPoint.

activation of cGAS, thereby facilitating efficient cGAMP production^[17] [Figure 2]. This cyclic dinucleotide (CDN) is a second messenger that engages the adaptor protein STING, thus initiating a signaling cascade.^[11] In addition, manganese ions (Mn^{2+}) have been shown to increase cGAS-mediated cGAMP synthesis by increasing the sensitivity of cGAS and stimulating cGAMP production, even in the absence of dsDNA.^[19]

Activation of STING by cGAMP

STING is a dimeric protein localized in the endoplasmic reticulum (ER) encoded by the transmembrane protein 173 gene. STING comprises a short N-terminal cytosolic region, four transmembrane helices, a cytosolic ligand-binding domain, and a C-terminal tail. The crystal structure of the cytoplasmic domain of STING has been elucidated, revealing a highly structured butterfly-like hydrophobic dimer.^[20,21] Upon cGAMP binding, STING undergoes a half-turn rotation and oligomerization, initiating its translocation from the ER to the ER–Golgi intermediate compartment and Golgi apparatus [Figure 2].

This trafficking process is facilitated by coatomer protein complex II and ADP-ribosylation factor (ARF) GTPases.^[22,23] In the Golgi/ER–Golgi intermediate compartment, STING recruits tank binding kinase 1 (TBK1), leading to the phosphorylation and activation of interferon regulatory factor 3 (IRF3) and nuclear factor kappa B (NF-κB), which are critical transcription factors for regulating immune responses^[24–26] [Figure 2].

Signaling pathways downstream of STING activation

The cGAS–STING signaling pathway can be transduced via three downstream signaling pathways, including STING–TBK1–IRF3, STING–TBK1/IκB kinases (IKKs)–NF-κB, and STING–PKR-like endoplasmic reticulum kinase (PERK)–eukaryotic initiation factor 2α (eIF2α) [Figure 2].

STING–TBK1–IRF3 signaling pathway

The STING–TBK1–IRF3 signaling pathway is a canonical cascade initiated upon STING activation. Once activated,

STING recruits TBK1 to its C-terminal tail, which harbors a highly conserved motif, initiating TBK1 autophosphorylation at Ser172 and subsequent phosphorylation of STING at Ser366 [Figure 2]. This phosphorylation event facilitates the recruitment of IRF3, where TBK1 further phosphorylates IRF3 at its C-terminus, promoting IRF3 dimerization, nuclear translocation, and transcriptional activation.^[27,28] Within the nucleus, IRF3 acts as a transcription factor, driving the transcription of IFN-Is and numerous IFN-stimulated genes^[29] [Figure 2]. This transcriptional activity is enhanced by coactivators such as CREB-binding protein/p300 and is coordinated with NF- κ B activation.^[30,31] In addition, the NOD-like receptor (NLR) family CARD domain containing 4, a key component of inflammasomes, facilitates the interaction between TBK1 and the E3 ubiquitin ligase Cbl proto-oncogene, leading to K63-linked polyubiquitination and activation of TBK1^[32] [Figure 2]. However, the precise mechanism and location of TBK1 recruitment to the STING complex remain to be elucidated.

STING–TBK1/IKKs–NF- κ B signaling pathway

The STING–TBK1/IKKs–NF- κ B signaling pathway is another critical pathway of the STING-mediated immune response. Canonical NF- κ B activation relies on IKKs, which phosphorylate, ubiquitinate, and target NF- κ B inhibitor- α for degradation, releasing the p65 and p50 subunits to translocate into the nucleus [Figure 2]. This nuclear translocation initiates the transcription of inflammatory genes and the production of proinflammatory cytokines.^[31,33] Several studies have indicated that TBK1 is crucial in activating NF- κ B.^[30,34] Specifically, sterol regulatory element-binding protein cleavage-activating protein (SCAP), a cholesterol sensor, recruits STING and TBK1 to the Golgi apparatus for activation^[34] [Figure 2]. However, STING-induced NF- κ B signaling appears to be less reliant on the kinase activities of TBK1 and IKKs in certain contexts, indicating potential redundancy in their roles during NF- κ B activation.^[35] The precise mechanisms underlying cGAS–STING-mediated NF- κ B activation remain an area of active investigation.

STING–PERK–eIF2 α signaling pathway

The STING–PERK–eIF2 α signaling pathway is a non-canonical cGAS–STING signaling cascade that operates independently of the canonical STING–TBK1–IRF3 signaling pathway.^[36] PERK is an ER-localized protein and a crucial effector of the unfolded protein response. PERK is directly activated by binding with cGAMP-bound STING at the ER via its intracellular domains [Figure 2]. This activation of PERK leads to the phosphorylation of eIF2 α , initiating translational programs associated with inflammation and cell survival.^[36] The evolutionarily conserved STING–PERK–eIF2 α signaling axis plays a critical role in cellular senescence and organ fibrosis^[36,37] [Figure 2].

cGAS–STING Signaling Pathway in Human Diseases

The role of the cGAS–STING signaling pathway in various diseases has been extensively studied. In this section,

we summarize the role of the cGAS–STING signaling pathway in neurological disorders, psychiatric disorders, digestive diseases, endocrine system diseases, circulatory system diseases, blood disorders, respiratory system diseases, urinary system diseases, reproductive system diseases, autoimmune diseases, pathogen infection, aging, and other diseases [Figure 3].

cGAS–STING signaling pathway in neurological disorders

The cGAS–STING signaling pathway can be activated in the nervous system and is implicated in various neurological diseases [Figure 4]. Below, we summarize the mechanisms of the cGAS–STING signaling pathway in different neurological disorders.

Mitochondrial dysfunction is a key driver of STING activation in the nervous system. Defects in mitophagy, which clears damaged mitochondria and protein aggregates, lead to the release of mtDNA into the cytoplasm [Figure 4]. mtDNA is recognized by the cGAS–STING signaling pathway, initiating downstream immune responses.^[38] For example, in Parkinson's disease (PD), mutations in the *Pink1* and *Parkin* genes impair mitophagy, causing the accumulation of damaged mitochondria and subsequent mtDNA release.^[39,40] Similarly, protein aggregates, such as mutant TAR DNA-binding protein 43 and superoxide dismutase 1, which are associated with amyotrophic lateral sclerosis (ALS), disrupt mitochondrial membrane integrity, promote mtDNA leakage, and activate the cGAS–STING signaling pathway.^[41] Protein aggregates characteristic of neurodegenerative diseases exacerbate mitochondrial dysfunction and lead to the release of mtDNA. In Alzheimer's disease (AD), tau protein impairs mitochondrial membrane integrity and facilitates mtDNA leakage and subsequent STING activation.^[42,43] Similarly, in Huntington's disease (HD), mutant huntingtin aggregates increase mtDNA release and cGAS-mediated inflammation in the striatum and cortex.^[44] Polyglutamine-binding protein 1 can act as a direct link between protein aggregates and STING activation. Polyglutamine-binding protein 1 recognizes polymerized tau in AD or mutant huntingtin in HDs, subsequently recruiting and activating the cGAS–STING signaling pathway.^[38,45] The above data highlights the complexity of protein aggregates in STING-driven neuropathology.

Cytoplasmic leakage of nuclear DNA fragments resulting from genomic instability is another significant activator of STING^[38] [Figure 4]. Disorders such as ataxia-telangiectasia (A-T) are classic examples of this mechanism. A-T is caused by mutations in the A-T-mutated gene, a key regulator of the DNA damage response. The loss of A-T-mutated function leads to the accumulation of dsDNA breaks and genomic instability. In this context, fragmented DNA escapes into the cytoplasm, triggering the cGAS–STING signaling pathway.^[46] Evidence from human induced pluripotent stem cell (iPSC)-derived cortical organoids from A-T patients shows that cytoplasmic genomic DNA activates the STING signaling pathway. In contrast, treatment with STING inhibitors reduces both inflammation and neurodegeneration.^[47] A similar phenomenon is observed in AD, where brain

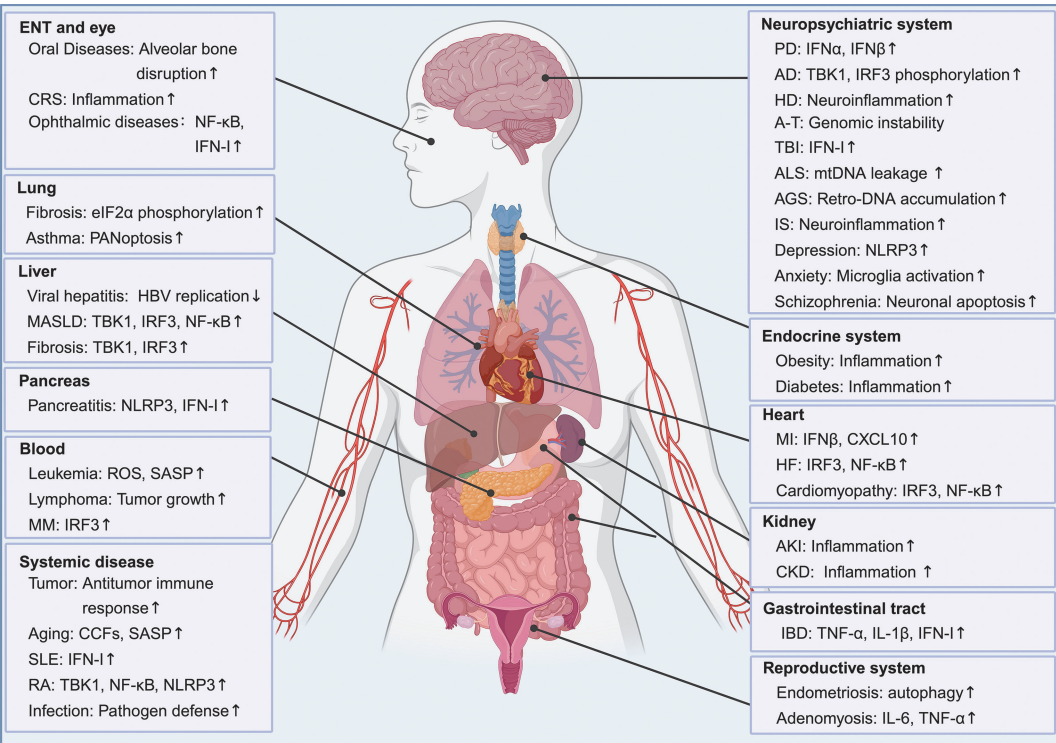


Figure 3: Human diseases associated with the cGAS–STING signaling pathway. The cGAS–STING signaling pathway is implicated in systemic disease processes, including autoimmunity, aging, infection, and cancer, as well as organ-specific disorders affecting the lungs, ENT and eyes, liver, pancreas, blood, neuropsychiatric system, endocrine system, heart, kidneys, gut, and reproductive system. The crucial upstream or downstream molecules are also shown. AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; AGS: Aicardi–Goutières syndrome; A-T: Ataxia–telangiectasia; AKI: Acute kidney injury; CCFs: Cytoplasmic chromatin fragments; cGAS: Cyclic GMP–AMP synthase; CKD: Chronic kidney disease; CRS: Chronic rhinosinusitis; CXCL10: C-X-C motif chemokine ligand 10; eIF2α: Eukaryotic initiation factor 2α; ENT: Ear, nose, throat; HBV: Hepatitis B virus; HD: Huntington's disease; HF: Heart failure; IBD: Inflammatory bowel disease; IFN: Interferon; IRF3: Interferon regulatory factor 3; IS: Ischemic stroke; MASLD: Metabolic dysfunction-associated steatotic liver disease; MI: Myocardial infarction; MM: Multiple myeloma; NF-κB: Nuclear factor kappa B; NLRP3: NOD-like receptor protein 3; PD: Parkinson's disease; RA: Rheumatoid arthritis; ROS: Reactive oxygen species; SASP: Senescence-associated secretory phenotype; SLE: Systemic lupus erythematosus; STING: Stimulator of interferon genes; TBI: Traumatic brain injury; TBK1: Tank binding kinase 1. ↑: Increase; ↓: Decrease. Created with BioRender.com.

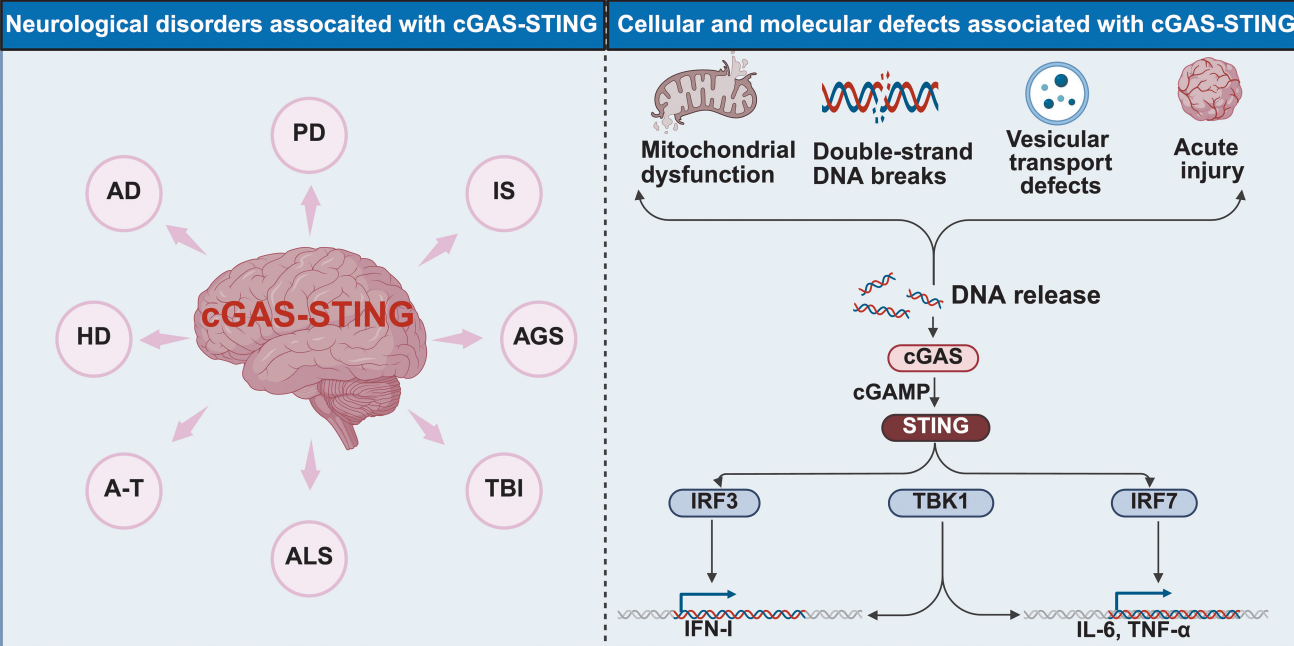


Figure 4: The cGAS–STING signaling pathway drives neurological disease progression via multiple mechanisms. Activation of the cGAS–STING signaling pathway contributes to the pathogenesis of multiple neurological disorders, including AD, PD, HD, A-T, ALS, TBI, IS, and AGS. Mitochondrial dysfunction, DNA damage, vesicular transport defects, and acute injury collectively activate the cGAS–STING signaling pathway, subsequently inducing type I interferon responses and inflammatory cascade activation. AD: Alzheimer's disease; AGS: Aicardi–Goutières syndrome; A-T: Ataxia–telangiectasia; ALS: Amyotrophic lateral sclerosis; cGAMP: Cyclic GMP–AMP; cGAS: Cyclic GMP–AMP synthase; HD: Huntington's disease; IRF: Interferon regulatory factor; IS: Ischemic stroke; PD: Parkinson's disease; STING: Stimulator of interferon genes; TBI: Traumatic brain injury; TBK1: Tank binding kinase 1. Created with BioRender.com.

tissue presents elevated levels of dsDNA breaks and impaired DNA repair capacity. These abnormalities are particularly pronounced in the cortex and hippocampus. In AD mouse models (e.g., *App/Ps1* transgenic mice), the levels of phosphorylated STING and downstream inflammatory markers (e.g., IFN-stimulated genes) are significantly increased, highlighting the involvement of STING in AD pathology.^[48] Moreover, markers of STING activation, including phosphorylated TBK1, IRF3, and IRF7, are elevated in AD models and patient samples^[49,50] [Figure 4]. In addition, in HD, cytoplasmic genomic DNA accumulation due to DNA repair deficits activates the cGAS–STING signaling pathway, contributing to neuroinflammation and neuronal loss.^[38]

Proper vesicle trafficking is essential for maintaining STING homeostasis [Figure 4]. Disruptions in this process delay STING degradation, leading to its chronic activation. For example, mutations in *Vps13c*, which are associated with familial PD, impair lysosomal lipid homeostasis and result in prolonged STING signaling.^[51] Similarly, *C9orf72* mutations, which are commonly observed in individuals with ALS and frontotemporal dementia, can disrupt autophagy–lysosome signaling pathways and cause hyperactivation of STING.^[52,53]

Acute injuries, such as traumatic brain injury (TBI) or ischemic stroke (IS), also trigger cGAS–STING signaling pathway activation [Figure 4]. These injuries induce the release of mtDNA into the cytoplasm, where it activates the signaling pathway. Elevated levels of cytoplasmic mtDNA have been observed in animal models of TBI and stroke, further supporting the involvement of STING in injury-induced neuroinflammation.^[54–56]

Under certain genetic conditions, such as Aicardi–Goutières syndrome (AGS), the activation of retrotransposons, such as long interspersed nuclear element-1 (LINE-1), contributes to STING activation. Nucleation mutations accumulating retroelement-derived DNA can activate the cGAS–STING signaling pathway, eventually leading to inflammation and neurological symptoms in AGS patients.^[57,58]

The activation of the STING signaling pathway in the nervous system is a common feature in many neurological diseases. The STING signaling pathway is driven by diverse mechanisms, including mitochondrial dysfunction, DNA damage, protein aggregation, and defects in cellular trafficking [Figure 4]. Understanding these signaling pathways provides critical insights into how STING contributes to neuroinflammation and offers potential therapeutic avenues for targeting STING in these disorders.

cGAS–STING signaling pathway in psychiatric disorders

Psychiatric disorders represent a major global health burden, with an estimated 970 million individuals affected worldwide.^[59,60] Increasing evidence implicates the cGAS–STING signaling pathway in the pathogenesis of various psychiatric conditions, including depression, anxiety, and schizophrenia^[61–64] [Figure 3]. The cGAS–STING

signaling pathway has emerged as a key mediator of neuroinflammation, influencing microglial activation and neuronal function.

Chronic stress induces depressive- and anxiety-like behaviors in murine models, accompanied by microglial activation and upregulation of the cGAS–STING signaling pathway in the basolateral amygdala [Figure 3].^[61,62] Furthermore, prenatal amoxicillin exposure disrupts the gut microbiota composition in offspring, impairing ARF1 N-myristoylation and subsequent STING degradation. This dysregulation leads to autophagic dysfunction, M1 microglial polarization, and depressive-like behaviors.^[63] In schizophrenia, innate immune hyperactivation and neuronal apoptosis are frequently observed. The human endogenous retrovirus W envelope glycoprotein triggers an antiviral innate immune response via the linc01930–cGAS–STING axis, promoting neuronal apoptosis and contributing to disease pathology^[64] [Figure 3].

Pharmacological inhibition of STING alleviates anxiety-like behaviors and suppresses microglial activation in chronic ethanol-exposed mice.^[65] Similarly, betaine attenuates DNA damage and mitochondrial dysfunction, blocking the cGAS–STING signaling pathway and restoring hippocampal neurogenesis in dextran sulfate sodium-treated mice, thereby mitigating depressive- and anxiety-like behaviors.^[66] In TBI models, STING-dependent interventions that reduce IFN-I signaling prevent prolonged microglial activation and cognitive impairment^[67,68] [Figure 3]. In addition, electroacupuncture exerts antidepressant effects in mice, likely through inhibition of the cGAS–STING–NOD-like receptor protein 3 (NLRP3) axis^[69] [Figure 3]. Interestingly, STING activation can also exert neuroprotective effects. The activated STING signaling pathway can increase microglial phagocytosis and suppress the release of the proinflammatory cytokines tumor necrosis factor (TNF)- α , interleukin (IL)-6, and IL-1 β in the brains of restraint stress mice, which further leads to antidepressant effects.^[62]

In summary, the current findings strongly support the involvement of the cGAS–STING signaling pathway in psychiatric disorders. However, the precise mechanisms remain unclear, with evidence suggesting that both proinflammatory and anti-inflammatory roles depend on the pathological context. Given its regulatory effects on neuroinflammation, microglial activation, and neuronal survival, STING represents a promising therapeutic target for psychiatric disorders.

cGAS–STING signaling pathway in digestive system diseases

cGAS–STING signaling pathway in gastroesophageal diseases

Esophagus cancer (EC)

EC ranks as the seventh most prevalent malignancy globally, with over 470,000 newly diagnosed cases annually.^[70] Histologically, EC is classified into two types: esophageal adenocarcinoma (EAC) and esophageal squamous

cell carcinoma (ESCC). Among these, ESCC is the sixth leading cause of cancer-related mortality worldwide.^[71] In ESCC, increased levels of cytosolic dsDNA have been shown to activate the cGAS–STING signaling pathway. However, the role of this signaling pathway in ESCC remains a subject of debate.^[72,73]

The p63 isoform acts as an oncogene in EC. Its depletion reduces cancer cell viability and increases STING expression, implicating the cGAS–STING axis in anti-tumor responses.^[72] Stress-induced mtDNA release via mitochondrial transcription factor A (TFAM) silencing activates cGAS–STING signaling, enhancing innate immunity.^[74] Conversely, reduced TFAM can activate this pathway, promoting autophagy and EC growth.^[73] Thus, cGAS–STING signaling exhibits a paradoxical role in EC development.

Radiotherapy for ESCC triggers DNA damage, cytokine release, inflammation, and tumor microenvironment (TME) alterations that can suppress immunity and promote invasion/metastasis.^[71] The intrinsic tumor cGAS–STING expression is crucial for radiation-induced immune cell activation within the TME, yet also recruits pro-tumorigenic M2 macrophages in ESCC.^[75] Mn²⁺ activates cGAS–STING, enhancing anti-tumor immunity,^[76] whereas MnSe₂-lipid enhances ESCC radiosensitivity by stimulating cGAS–STING-mediated immunity and chemodynamic therapy.^[77] Therefore, optimizing ESCC chemoradiotherapy requires maximizing the therapeutic benefits of cGAS–STING while minimizing its detrimental effects.

Gastric cancer (GC)

GC is the fifth most prevalent malignancy globally and the third leading cause of cancer-related mortality, and its risk sharply increases among men after the age of 40 years, leading to a significant disparity in burden between men and women.^[78] In human GC tissues, STING expression is significantly reduced in a tumor node metastasis stage-dependent manner, and *Sting* knockdown enhances GC cell survival.^[79] In HER2-positive GC, HER2 signaling may inhibit STING activation in tumor cells, thereby suppressing immune cell activation in the TME.^[80] The accumulation of cytosolic DNA activates the STING signaling pathway in GC.^[81] A high level of STING in tumor-associated macrophages predicts poor survival of GC patients. Both *Sting* knockdown and activation by 2'3'-c-GAMP promote the differentiation of tumor-associated macrophages into a proinflammatory subtype and induce the apoptosis of GC cells via the IL6R–JAK–IL24 signaling pathway.^[82] When activated in different cells, the cGAS–STING signaling pathway may promote or suppress the development of gastroesophageal cancers.

In summary, the cGAS–STING signaling pathway has dual roles in gastroesophageal cancers. When activated by cytosolic DNA, the cGAS–STING signaling pathway elicits innate immune responses and exerts anti-tumor effects. However, its activation can also promote tumor growth. The role of this signaling pathway depends on the cell type activated (cancer or immune cells), the

disease stage, and the treatment context, such as chemoradiotherapy.

cGAS–STING signaling pathway in intestinal diseases

Inflammatory bowel disease (IBD)

IBD, encompassing ulcerative colitis (UC), Crohn's disease (CD), and unclassified IBD (IBDU), is a chronic relapsing gastrointestinal disorder. The cGAS–STING pathway is activated in the colonic mucosa of UC patients^[83] [Figure 5]. Myeloid-specific *Sting* deletion in mice inhibits macrophage maturation, dendritic cell (DC) activation, and proinflammatory Th1/Th17 cell proliferation, protecting against acute/chronic colitis and colitis-associated carcinoma^[84] [Figure 5]. In IBD patients, reduced DEAH-box helicase 9 expression triggers genomic instability and cGAS–STING-driven inflammation, impairing intestinal stem cell function and contributing to pathogenesis.^[85] Heterochromatin protein 1γ (HP1γ) maintains nuclear integrity and genomic stability in enterocytes; its dysfunction enhances cGAS–STING activity, promoting intestinal inflammation.^[16] Exosomal dsDNA exacerbates CD by activating cGAS–STING, correlated with disease severity,^[86] whereas mtDNA from damaged epithelial cells activates STING in DCs, upregulating IL-12 family cytokines^[84] [Figure 5]. Conversely, *Sting* deletion in established tumors promotes immunosuppression and tumor growth.^[84] These findings underscore the role of STING in colitis pathogenesis and treatment.

Emerging evidence indicates that the STING signaling pathway possesses anti-inflammatory properties, suggesting the potential of STING agonists as therapeutic agents for IBD.^[87,88] Specifically, STING attenuates the pathogenic effects of Th1 cells in colitis by increasing the expression of the anti-inflammatory cytokine IL-10.^[87] Furthermore, STING1 can translocate to the nucleus and activate the aryl hydrocarbon receptor; the interaction between nuclear STING1 and the aryl hydrocarbon receptor protects against intestinal pathology and dysbiosis in mice.^[88] Therefore, further research is warranted to clarify the dual roles of the cGAS–STING signaling pathway in modulating both proinflammatory and anti-inflammatory responses in IBD.

IBD is characterized by an aberrant immune response to the intestinal microbiota. Dysbiosis exacerbates colitis by promoting the ubiquitination and accumulation of STING in myeloid cells^[89] [Figure 5]. Gut microbiota-derived extracellular vesicles induce epithelial damage and inflammatory responses in IBD via the cGAS–STING signaling pathway.^[90] STING enhances intestinal immunoglobulin A production by modulating acetate-producing bacteria.^[91] Fecal microbiota transplantation effectively treats dextran sulfate sodium-induced colitis in a STING-dependent manner. Fecal microbiota transplantation regulates the differentiation of intestinal Th17 cells, macrophages, splenic Th1 and Th2 cells, and mesenteric lymph node Th1 cells through the STING signaling pathway [Figure 5]. This regulation leads to the downregulation of colonic M1/M2 and splenic Th1/Th2 cell ratios, which

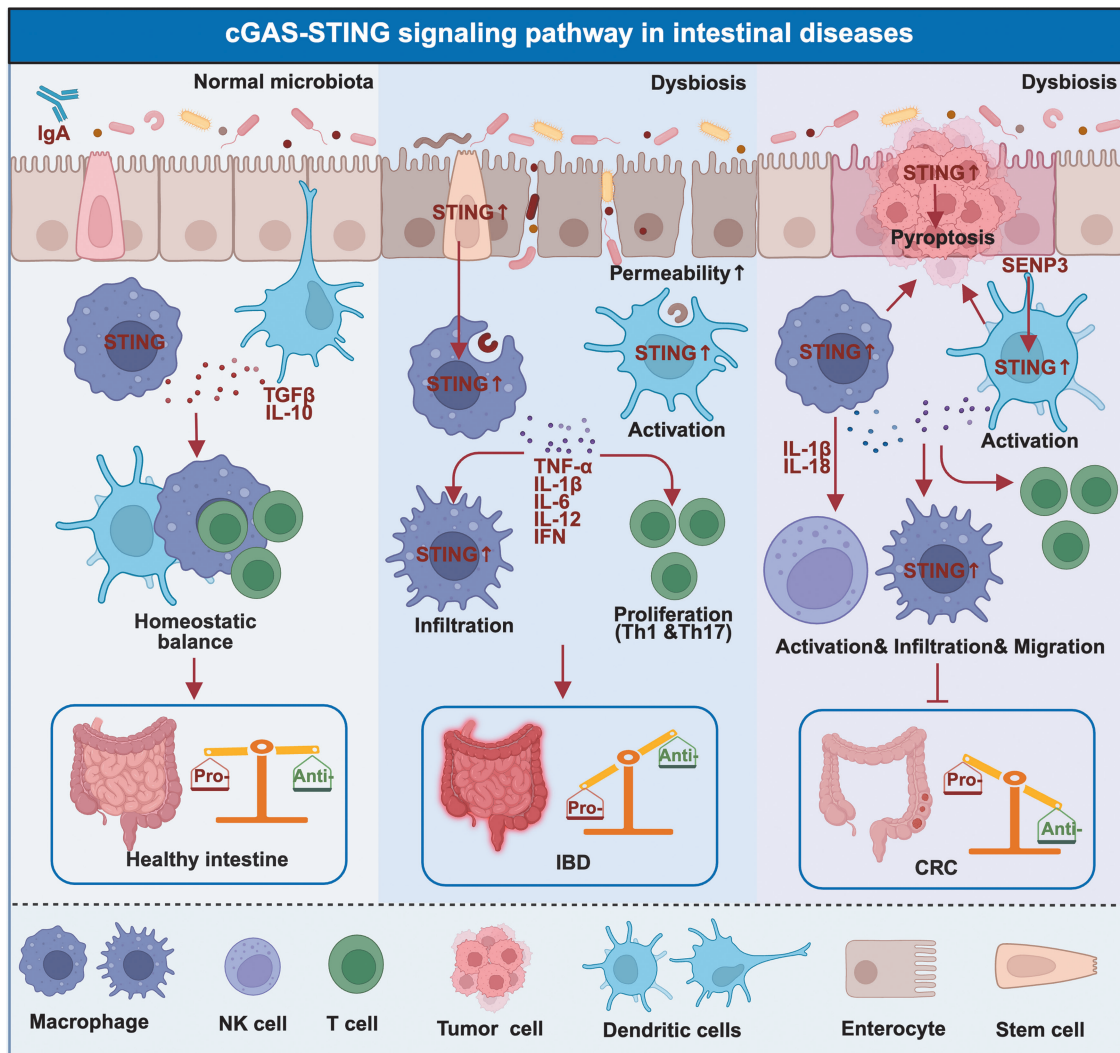


Figure 5: The cGAS–STING signaling pathway is crucial in intestinal disease pathogenesis. The cGAS–STING signaling pathway regulates intestinal homeostasis by maintaining a delicate balance between microbial surveillance and inflammatory responses, while its dysregulation contributes to the pathogenesis of IBD and CRC. Anti-: Inhibit disease progression; cGAS: Cyclic GMP–AMP synthase; CRC: Colorectal cancer; IBD: Inflammatory bowel disease; IgA: Immunoglobulin A; Pro-: Promote disease progression; SENP3: SUMO-specific protease 3; STING: Stimulator of interferon genes; Th: T helper cell. Created with BioRender.com.

are essential for restoring immune homeostasis in the inflamed intestinal mucosa.^[92] Consequently, restoring dysbiosis via STING-dependent mechanisms represents a promising therapeutic strategy for IBD.

Colorectal cancer (CRC)

CRC is the third most commonly diagnosed cancer worldwide. Among the digestive system cancers, colorectal cancer had the most severe burden in terms of both incidence and mortality.^[93] The cGAS–STING signaling pathway has been recognized as crucial for preventing tumorigenesis and enhancing the efficacy of various anti-tumor therapies, including immune checkpoint therapy, chemotherapy, and radiotherapy.^[84,94] *Sting*-deficient mice exhibit increased susceptibility to colitis-associated carcinoma due to reduced pyroptosis of tumor cells^[95] [Figure 5]. In addition, STING promotes the production of IL-18 and IL-1β by macrophages via the NLRP3 inflammasome, thereby optimizing the antitumor function

of natural killer (NK) cells^[96] [Figure 5]. DCs are critical for initiating antitumor immune responses. DC-derived reactive oxygen species (ROS) trigger SUMO-specific protease 3 accumulation and promote STING-dependent cytosolic DNA sensing, thereby enhancing DC antitumor functions in the TME^[94] [Figure 5]. Barrier-to-autointegration factor 1 (BANF1) naturally inhibits cGAS activity on genomic self-DNA. *Banf1* knockout activates antitumor immune responses mediated by the cGAS–STING signaling pathway.^[97] Collectively, activating the cGAS–STING signaling pathway is essential for augmenting the antitumor immune response of macrophages and DCs in CRC [Figure 5].

Emerging evidence underscores the critical role of the microbiota in modulating responses to cancer therapies.^[98–100] Specifically, the gut microbiota has been shown to colonize tumor sites and enhance immunotherapy efficacy through STING signaling.^[99] The gut microbiota-associated metabolite methylglyoxal amplifies radiotherapy-induced

activation of the cGAS–STING signaling pathway by increasing the number of dsDNA breaks.^[101] Furthermore, *Fusobacterium nucleatum* has been found to enhance the antitumor response to programmed cell death protein 1 (PD-1)/ligand 1 (PD-L1) checkpoint blockade by activating STING signaling, which induces PD-L1 expression and promotes the accumulation of IFN- γ ⁺ CD8⁺ tumor-infiltrating lymphocytes.^[98] Consistently, oral administration of *Lactobacillus rhamnosus* GG has been demonstrated to augment the antitumor effects of anti-PD-1 immunotherapy by increasing the infiltration of DCs and T cells into tumors. In DCs, *Lactobacillus rhamnosus* GG triggers IFN- β production through the cGAS–STING–TBK1–IRF7 signaling axis.^[100]

In summary, the cGAS–STING signaling pathway has dual effects on intestinal diseases. In IBD, it can be activated by host DNA damage or dysbiosis, driving inflammation. However, it also has anti-inflammatory and barrier-protective effects through IL-10 induction, microbiota metabolism modulation, and increased IgA production. In CRC, the cGAS–STING signaling pathway can suppress tumorigenesis but may also be exploited by the TME to mediate immunosuppression. Microbial modulation could serve as a complementary strategy for IBD and cancer therapeutics.

cGAS–STING signaling pathway in hepatic diseases

Viral hepatitis

Hepatitis B virus (HBV) is an enveloped, partially dsDNA virus that preferentially replicates within hepatocytes. The ability of HBV to evade the host immune response is a pivotal factor in the pathogenesis of hepatitis B.^[102,103] Upon infection, the HBV genomic DNA within the nucleocapsid is transported into the nucleus of hepatocytes and converted into covalently closed circular DNA (cccDNA), which serves as the transcriptional template for viral RNA synthesis [Figure 6]. These HBV RNAs fail to stimulate an immune response in immunocompetent myeloid cells. In contrast, HBV DNA from viral particles and replication intermediates can be detected via the cGAS–STING signaling pathway, thereby triggering an immune response^[104] [Figure 6]. Notably, enhanced disassembly of mature nucleocapsids in the cytoplasm promotes cccDNA amplification without activating the cGAS–STING-mediated innate immune response in hepatocytes.^[105] The encapsidation of HBV DNA by the viral capsid, combined with the relatively low expression levels of cGAS and STING in hepatocytes, likely facilitates immune evasion by HBV during infection.^[103,104] Agonist-induced STING activation in macrophages inhibits cccDNA-mediated transcription and HBV replication in hepatocytes, thereby mitigating liver injury and fibrosis in chronic cccDNA mouse models^[8] [Figure 6]. HBV infection elevates the expression of histone acetyltransferase 1. HBV-elevated histone acetyltransferase 1 regulates the cGAS–STING signaling pathway and IFN-I signaling through acetylation of histones H4K5 and H4K12, thereby modulating viral innate immune evasion.^[102] Thus, targeting the cGAS–STING signaling pathway may

provide a potential therapeutic strategy to enhance the host immune response against HBV [Figure 6].

Metabolic dysfunction-associated steatotic liver disease (MASLD) and liver fibrosis

MASLD encompasses a spectrum of pathological states, ranging from simple steatosis (MASL) to metabolic dysfunction-associated steatohepatitis (MASH) and subsequent liver fibrosis. Emerging evidence highlights the cGAS–STING signaling pathway as a pivotal factor in the pathogenesis of MASLD^[25,36,106] [Figure 6]. Specifically, cGAS can recognize aberrant DNA and activate STING to trigger immune responses that influence lipid metabolism and inflammatory pathways, leading to hepatic fat accumulation and hepatocyte injury.^[107]

MASL is characterized by hepatic steatosis and lipotoxicity without significant inflammation or fibrosis. The STING–IRF3 axis is implicated in hepatocyte injury and dysfunction through disruptions in glucose and lipid metabolism, as well as the induction of inflammation and apoptosis^[25] [Figure 6]. STING expression is elevated in MASL livers, promoting lipolysis in adipocytes and lipid uptake and synthesis in hepatocytes^[34,107] [Figure 6]. Macrophage-specific *Scap* deletion attenuates Paigen diet-induced metaflammation and ectopic lipid deposition by reducing hepatic STING–NF- κ B signaling pathway.^[34]

MASH is a progressive form of MASLD characterized by liver steatosis, inflammation, hepatocellular damage, and varying degrees of fibrosis. The sterile inflammation mediated by the cGAS–STING signaling pathway is associated with MASH. In sterile inflammatory liver injury, impaired mitophagy in aged macrophages leads to mtDNA leakage into the cytosol, activating the STING signaling pathway^[15] [Figure 6]. MASH patients exhibit elevated levels of ROS and mtDNA damage,^[108] with mtDNA translocating to the cytoplasm to activate cGAS and immune responses.^[109] Palmitic acid-induced mitochondrial damage and subsequent mtDNA leakage activate the cGAS–STING–IRF3 signaling pathway, leading to endothelial activation and inflammation^[110] [Figure 6]. Kupffer cells and macrophages contribute to MASH by secreting proinflammatory cytokines such as transforming growth factor- β , IL-6, and TNF- α .^[111–113] Increased STING activation in macrophages during MASH promotes a proinflammatory state, which enhances hepatic fat deposition and activates hepatic stellate cells, driving fibrosis^[113] [Figure 6].

Liver fibrosis is a wound-healing response to chronic injury characterized by excessive accumulation of the extracellular matrix. The cGAS–STING signaling pathway activation exacerbates intrahepatic inflammation and promotes fibrosis progression.^[114] In addition to the canonical cGAS–STING–TBK1–IRF3 signaling pathway, a noncanonical cGAS–STING–PERK–eIF2 α signaling pathway involving cellular senescence has also been implicated in liver fibrosis pathogenesis^[36,37] [Figure 6]. Cytoplasmic chromatin fragments (CCFs) from senescent cells trigger the senescence-associated secretory phenotype (SASP) via the cGAS–STING signaling pathway.^[115,116]

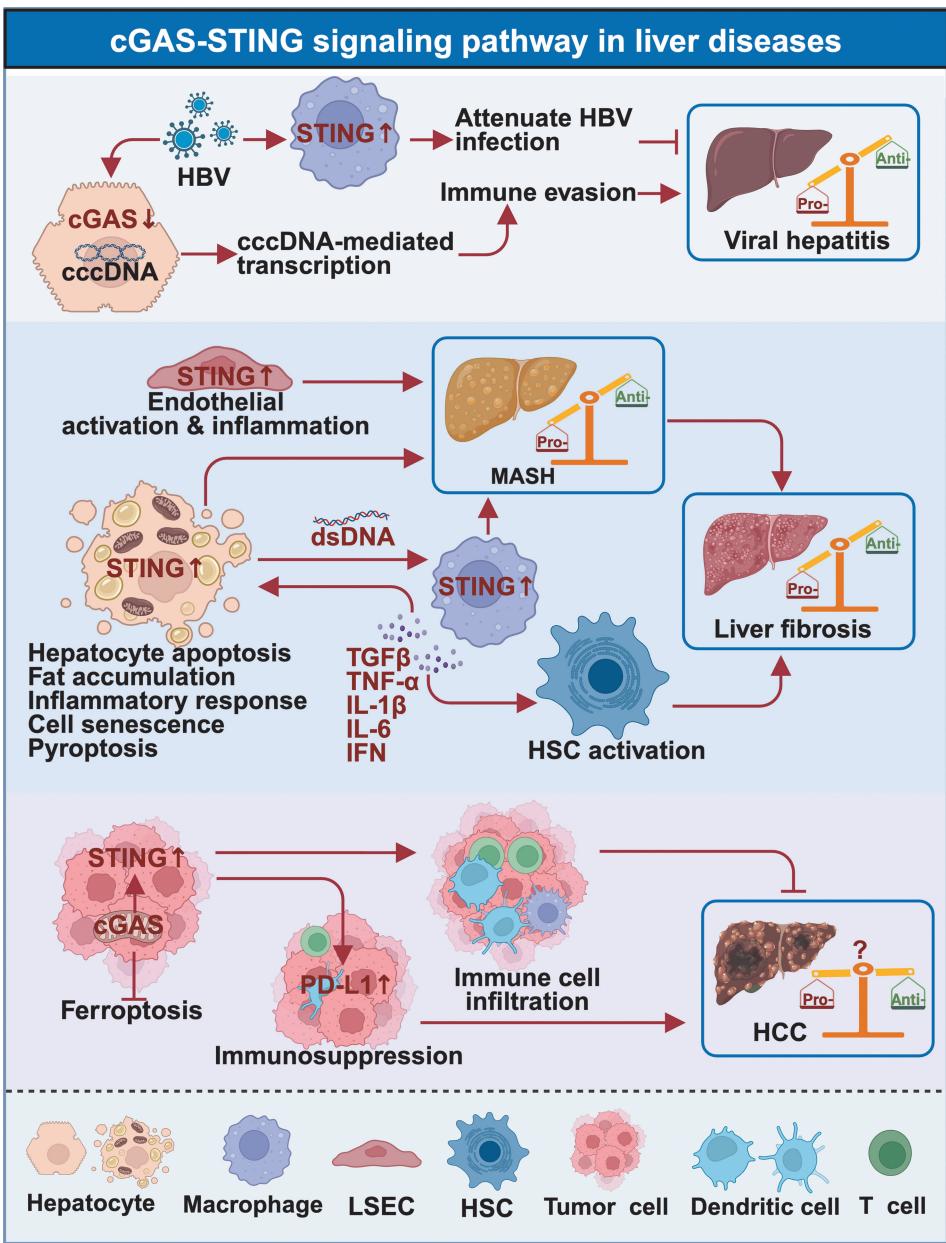


Figure 6: The cGAS–STING signaling pathway exhibits diverse roles across liver diseases. The cGAS–STING signaling pathway plays complicated roles in liver diseases. It inhibits HBV infection in hepatitis B patients, while its pro-inflammatory effects promote the development and progression of MASLD and liver fibrosis. In hepatocellular carcinoma, the cGAS–STING signaling pathway demonstrates a dual role, exerting both pro-tumorigenic and anti-tumorigenic effects. Anti-: Inhibit disease progression; cGAS: Cyclic GMP-AMP synthase; cccDNA: Covalently closed circular DNA; dsDNA: Double-stranded DNA; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HSC: Hepatic stellate cell; IFN: Interferon; IL: Interleukin; LSEC: Liver sinusoidal endothelial cell; MASH: Metabolic dysfunction-associated steatohepatitis; MASLD: Metabolic dysfunction-associated steatotic liver disease; PD-L1: Programmed cell death protein 1 ligand; Pro-: Promote disease progression; STING: Stimulator of interferon genes. Created with BioRender.com.

Moreover, activating the cGAS–STING–NLRP3 signaling pathway can accelerate liver fibrosis in a hepatocyte pyroptosis-dependent manner^[117] [Figure 6]. These findings indicate that the cGAS–STING signaling pathway is critical in determining liver cell fate, including senescence and pyroptosis, during the progression of liver fibrosis.

Liver injury induced by alcohol and ischemia/reperfusion (I/R)

Exposure to alcohol, drugs, radiation, and I/R can induce liver injury. In alcoholic liver disease (ALD), activation of the cGAS–STING signaling pathway is positively

associated with the severity of ALD. The cGAS–STING signaling pathway triggers IRF3 in hepatocytes and adjacent tissues via gap junction intercellular communication, thereby exacerbating alcohol-induced liver injury.^[118] Liver-specific dynamin-related protein 1 (DRP1) is an essential regulator of mitochondrial fission and is pivotal for maintaining cellular homeostasis. In alcohol-fed *L-DRP1* knockout mice, the absence of DRP1 leads to increased cytosolic mtDNA levels and mitochondrial dysfunction, which subsequently activates the cGAS–STING signaling pathway and contributes to liver injury.^[119] The expression of STING is upregulated in monocyte-derived macrophages and contributes to liver inflammation

during I/R injury.^[120,121] *Sting* knockdown mitigates calcium-dependent macrophage caspase 1–gasdermin D-mediated I/R injury.^[122] Notably, the activation of the cGAS–STING signaling pathway in liver I/R injury is caused primarily by the liberation of mtDNA rather than nuclear DNA.^[123] Collectively, these findings indicate that the inhibition of STING may provide a protective effect against liver I/R injury.

Hepatocellular carcinoma (HCC)

HCC is the third leading cause of cancer-related mortality globally, with a 5-year relative survival rate of approximately 18%. The key risk factors for HCC include viral hepatitis, alcohol consumption, and nonalcoholic fatty liver disease.^[124] The role of the cGAS–STING signaling pathway in HCC is complex and multifaceted. Most studies suggest that cGAS–STING signaling pathway activation is crucial for HCC progression and is associated with poor prognosis.^[125,126] Specifically, mitochondrion-localized cGAS protects HCC cells from ferroptosis [Figure 6]. Without cGAS, tumor growth is suppressed via mitochondrial ROS accumulation and ferroptosis.^[125] In addition, activation of the cGAS–STING signaling pathway induces PD-L1 expression via the STING–IRF3–Signal transducer and activator of transcription 1 (STAT1) signaling pathway, leading to immunosuppression and facilitating tumorigenesis and tumor progression^[9] [Figure 6]. Conversely, cGAS is significantly downregulated in clinical HCC tissues, and its dysregulation contributes to HCC progression through cGAMP synthase.^[127] In addition, activation of the cGAS–STING signaling pathway enhances immune cell infiltration in HCC tissues, thereby exerting an antitumor effect^[128,129] [Figure 6].

In summary, the cGAS–STING signaling pathway plays a dual, context-dependent role in hepatic pathophysiology. Although the cGAS–STING signaling pathway is essential for innate immune defense against pathogens such as HBV, its chronic or dysregulated activation significantly contributes to pathology in sterile inflammatory conditions (e.g., MASLD/MASH, fibrosis, ALD, and I/R injury). In HCC, the cGAS–STING signaling pathway promotes tumor progression through immunosuppression and ferroptosis resistance but potentially enables antitumor immunity when appropriately modulated. This complexity necessitates disease- and stage-specific therapeutic strategies targeting the cGAS–STING signaling pathway. Future interventions require precise cell-type targeting (e.g., hepatocytes, macrophages, and hematopoietic stem cells) or modulation of specific downstream effectors to maximize therapeutic efficacy while minimizing detrimental inflammation and fibrosis.

cGAS–STING signaling pathway in pancreatic diseases

Pancreatitis

Acute pancreatitis (AP) is a severe inflammatory disease characterized by acinar cell death and the subsequent release of inflammatory mediators. In AP mouse models,

the STING protein is activated by DNA released from dying acinar cells, thereby activating the cGAS–STING signaling pathway in macrophages [Figure 7]. The cGAS–STING signaling pathway seems pivotal in initiating pancreatic inflammation.^[130] Extracellular vesicles derived from M1 macrophages can penetrate pancreatic β cells and fuse with their mitochondria, resulting in lipid peroxidation and mitochondrial disruption. This process releases mtDNA into the cytosol, further activating the STING signaling pathway and inducing apoptosis^[131] [Figure 7]. In addition, high-iron diets or depletion of the antioxidant enzyme glutathione peroxidase 4 can activate the STING signaling pathway, promoting macrophage activation and exacerbating experimental pancreatitis.^[132] Severe acute pancreatitis-associated acute lung injury (SAP-ALI) is a severe complication of AP. Upregulated STING signaling can promote NLRP3 inflammasome-mediated pyroptosis in macrophages and increase the serum levels of IL-6, IL-1 β , and TNF- α , thereby aggravating SAP-ALI.^[24] These findings indicate that STING signaling in macrophages is pivotal in promoting inflammatory responses and AP progression.

Chronic pancreatitis (CP) is an inflammatory disease characterized by progressive fibrosis, leading to exocrine and endocrine dysfunction of the pancreas. Unlike in AP, STING activation in CP reduces pancreatic inflammation and fibrosis, whereas its absence exacerbates this disease. Mechanistically, STING deletion is associated with increased infiltration of Th17 cells into the pancreas.^[133]

Pancreatic cancer

Pancreatic cancer is the seventh leading cause of cancer-related death worldwide.^[134] Pancreatic cancer is an incurable malignant disease with an extremely poor prognosis and a complex TME.^[135] Approximately 90% of pancreatic cancers are pancreatic ductal adenocarcinomas (PDACs).^[134] Chromosomal instability promotes aggressive tumor growth, which is characterized by early dissemination and metastasis in a STING-dependent manner.^[136] STING activation results in macrophage infiltration and activation in Kras-driven PDAC in mice.^[132] Despite the immunosuppressive nature of pancreatic cancer, several studies have shown that activating STING signaling promotes antitumor immunity.^[135,137–139] SMAD4, a key mediator of transforming growth factor- β signaling, is mutated or deleted in 20% of PDAC cases and significantly affects cancer development. *Smad4* deficiency significantly increases tumor cell immunogenicity by promoting spontaneous DNA damage and stimulating STING-mediated IFN-I signaling^[139] [Figure 7]. Activation of the cGAS–STING signaling pathway and proinflammatory signaling also activate macrophages and NK cells, further inhibiting tumor growth^[140] [Figure 7]. In addition, A-T and Rad3-related protein inhibition suppress PDAC tumor growth by enhancing IFN signaling through tumor cell-intrinsic STING activation,^[141] which depends on C-X-C motif chemokine receptor 3 expression.^[138] These studies suggest that STING agonists may serve as promising therapeutic strategies for pancreatic cancer.

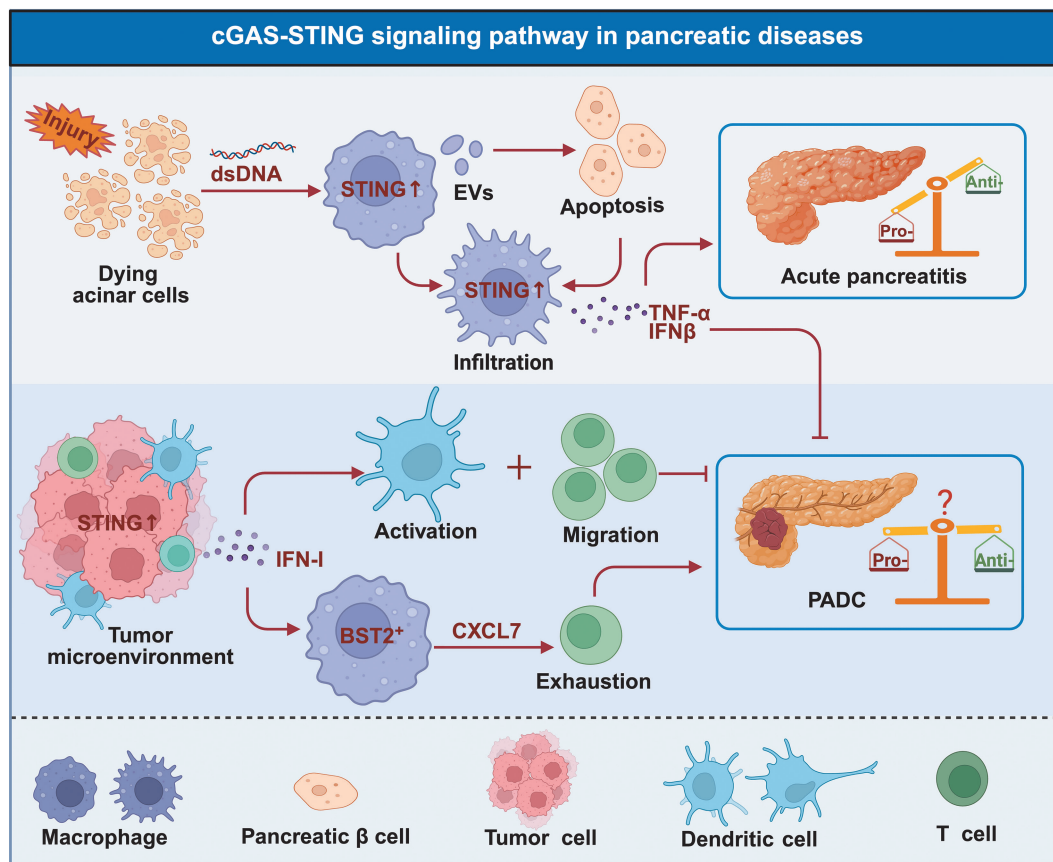


Figure 7: The cGAS–STING signaling pathway plays a crucial role in pancreatic diseases. Research on the cGAS–STING signaling pathway in pancreatic diseases has focused primarily on AP and PDAC. In AP, cGAS–STING serves as a potent driver of inflammation and organ damage. In PDAC, STING activation typically promotes antitumor immunity and has therapeutic potential. AP: Acute pancreatitis; Anti-: Inhibit disease progression; BST2⁺ macrophage: Bone marrow stromal antigen 2-positive macrophage; cGAS: Cyclic GMP–AMP synthase; CXCL7: C-X-C motif ligand 7; dsDNA: Double-stranded DNA; EV: Extracellular vesicle; IFN-I: Type I interferon; PDAC: Pancreatic ductal adenocarcinoma; Pro-: Promote disease progression; STING: Stimulator of interferon genes. Created with BioRender.com.

Pancreatic tumors are often referred to as “cold” tumors due to their immunosuppressive microenvironment, presenting significant challenges for immunotherapy.^[142] In PDAC models, murine STING agonists increase inflammatory cytokine and chemokine production, facilitating T-cell migration, enhancing DC maturation, and augmenting the quantity and functionality of tumor-infiltrating cytotoxic T cells [Figure 7]. These effects collectively reverse tumor immune suppression.^[143] Moreover, MEK inhibition potentiates the ability of STING agonists to induce IFN-I-dependent cell death and promote tumor regression.^[144] CD11b agonists activate the STING/STAT/IFN signaling pathways and repress NF-κB in pancreatic cancer, leading to tumor cell death.^[145] However, clinical trials of STING agonist monotherapy have faced significant challenges related to tumor resistance. Specifically, STING activation contributes to tumor resistance by inducing IL-35, which enhances regulatory B cell function and suppresses NK cell responses.^[142]

In summary, research on the cGAS–STING signaling pathway in pancreatic diseases has focused primarily on AP and PDAC. In AP, cGAS–STING serves as a potent driver of inflammation and organ damage. In PDAC, STING activation typically promotes antitumor immunity and has therapeutic potential.

cGAS–STING signaling pathway in endocrine system diseases

Obesity and its related metabolic diseases, such as diabetes, have become a significant societal burden. The cGAS–STING signaling pathway has been identified as a critical player in the development of obesity-related inflammation and insulin resistance [Figure 3]. Disulfide-bond A oxidoreductase-like protein (DsbA-L), a key molecule responsible for maintaining mitochondrial integrity in adipose tissue, has been shown to suppress cGAS–STING activation. *DsbA-L* deficiency promotes inflammation and insulin resistance by activating the cGAS–cGAMP–STING signaling pathway.^[146] In addition, the endocytosis of apoptotic bodies containing self-DNA by conventional type 1 DCs in white adipose tissue drives STING-dependent IL-12 production, further exacerbating inflammation^[147] [Figure 3]. These findings highlight the cGAS–STING signaling pathway as a potential therapeutic target in obesity and its metabolic complications.

cGAS–STING signaling pathway in circulatory system diseases

Myocardial infarction (MI)

MI represents a life-threatening form of coronary heart disease, with the most prominent pathological change

being ischemic injury to cardiomyocytes. This ischemic injury induces an inflammatory response and infiltration of innate immune cells, including macrophages.^[148] Macrophages, exhibiting plasticity, dynamically regulate both destructive and reparative processes post-MI through distinct phenotypic switching^[149] [Figure 8]. Infarct expansion and adverse fibroblast remodeling of cardiac fibroblasts occur at a destructive stage mediated by M1 macrophages and deteriorate heart function.^[150] IR injury can exacerbate cellular apoptosis and ROS accumulation.^[151] The mitochondria are structurally and functionally damaged in ischemic and hypoxic conditions, further aggravated by oxidative stress.^[152] The cGAS–STING signaling pathway in macrophages can detect mtDNA release and trigger inflammation through M1 macrophage polarization^[153] [Figure 8]. The downstream reactions of IFN-Is can cause cellular apoptosis and cardiac fibrosis via IFN- β and CXCL10 production^[154] [Figure 8]. Applying STING inhibitors alleviates cardiac contractile function and remodeling by reducing the inflammatory response after MI.^[154,155] Emerging therapeutic strategies targeting the cGAS–STING signaling

pathway have recently been proposed to reduce oxidative damage and regulate macrophage polarization, thereby accelerating cardiac repair.^[153]

Heart failure (HF)

HF is a pervasive global health challenge characterized by cardiac remodeling, which involves cardiac structural, compositional, and cellular abnormalities that impair heart function.^[156] Inflammatory cell infiltration and cytokine production have a complex and bidirectional relationship with cardiac remodeling in HF.^[157] Recent studies have shed light on the intricate relationship between the cGAS–STING signaling pathway and HF. In overload HF animal models induced by transverse aortic constriction, the cGAS–STING signaling pathway is activated following cardiomyocyte apoptosis and DNA leakage as damage-associated molecular patterns^[158] [Figure 8]. Dynamic observations revealed fluctuations in cGAS–STING expression in the HF model. These findings suggest a critical role of the cGAS–STING pathway in HF, correlated with the innate

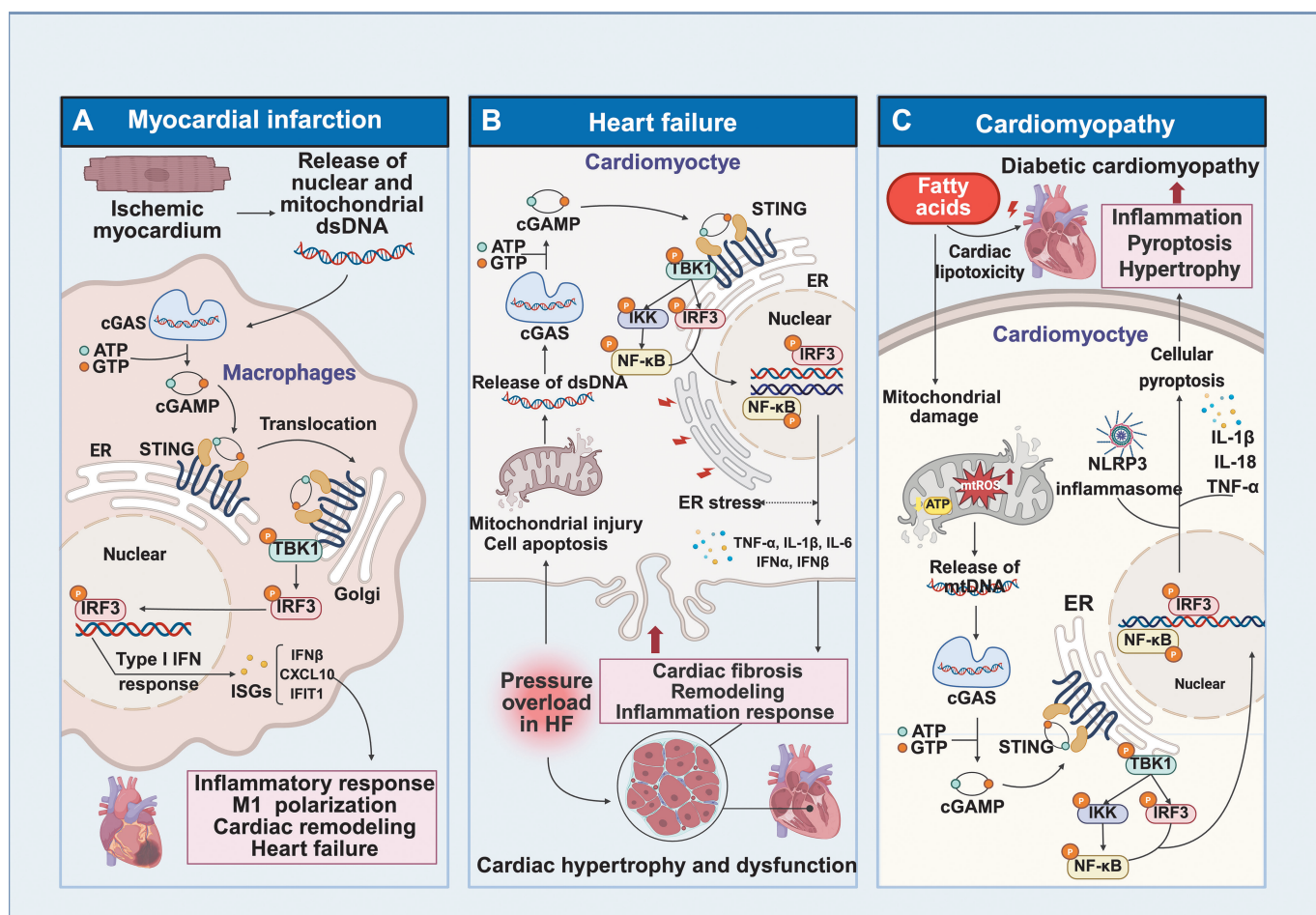


Figure 8: Activation of the cGAS–STING signaling pathway drives the progression of cardiovascular diseases. The cGAS–STING signaling pathway contributes to cardiovascular pathogenesis through distinct mechanisms: (A) Exacerbates ischemia-reperfusion injury by promoting proinflammatory M1 macrophage polarization to induce myocardial infarction. (B) Drive ventricular remodeling via fibrosis-mediated chronic inflammation to promote heart failure. (C) Promotion of cardiomyopathy progression through inflammation and cardiomyocyte pyroptosis. ATP: Adenosine triphosphate; cGAS: Cyclic GMP-AMP synthase; cGAMP: Cyclic GMP-AMP; CXCL10: C-X-C motif ligand 10; dsDNA: Double-stranded DNA; ER: Endoplasmic reticulum; GTP: Guanosine triphosphate; HF: Heart failure; IFIT1: Interferon-induced protein with tetratricopeptide repeats 1; IFN: Interferon; IKK: Inhibitor of NF- κ B; IL: Interleukin; IRF3: Interferon regulatory factor 3; ISGs: Interferon-stimulated genes; mtDNA: Mitochondrial DNA; NF- κ B: Nuclear factor kappa B; NLRP3: NOD-like receptor protein 3; STING: Stimulator of interferon genes; TBK1: Tank binding kinase 1; TNF- α : Tumor necrosis factor α . Created with BioRender.com.

immune-mediated short-term adaptation phase following early myocardial injury^[159] [Figure 8]. The cGAS–STING signaling pathway and downstream NF- κ B and IRF3, along with cytokines including IL-6, IL-1 β , monocyte chemoattractant protein-1, and TNF- α , might regulate the early inflammatory response and promote myocardial fibrosis and cardiomyocyte hypertrophy during HF^[160–162] [Figure 8]. Moreover, cardiomyocytes exhibit robust metabolic activity, characterized by pronounced metabolic flexibility and high mitochondrial density.^[163] HF is accompanied by metabolic reprogramming and derangements, including altered substrate utilization, diminished oxidative metabolism, and lipid accumulation.^[163] Cholesterol exacerbates lipotoxicity in cardiomyocytes via various regulatory mechanisms involved in cholesterol homeostasis.^[164] Enhancing bile acid synthesis and excretion is a key part of cholesterol metabolism. Bile acid intermediates can trigger mtDNA release and activate the cGAS–STING signaling pathway, thus promoting HF via the myocardial inflammation response. Overall, the activation of the cGAS–STING signaling pathway and downstream inflammatory cascades may represent a promising therapeutic strategy for preventing myocardial remodeling in HF [Figure 8].

Cardiomyopathy

Cardiomyopathies are a heterogeneous group of myocardial diseases characterized by mechanical and/or electrical dysfunction.^[165] Recently, emerging studies have revealed an association between the cGAS–STING signaling pathway and cardiomyopathy progression, with a particular focus on diabetic cardiomyopathy (DCM). Lipotoxicity is a pivotal mechanism underlying DCM development due to cardiac metabolic abnormalities. The diabetic heart is characterized by a metabolic preference for fatty acids (FAs) as substrates, driven by elevated circulating free FA levels, increased FA uptake, and disrupted glucose utilization.^[166] The cGAS–STING signaling pathway provides evidence linking lipotoxicity, mitochondrial damage, inflammatory responses, and DCM progression [Figure 8]. The activation of the cGAS–STING signaling pathway is triggered by mitochondrial dysfunction and mtDNA leakage, with IRF3 and NF- κ B acting as key downstream promoters of sterile inflammation in DCM^[167,168] [Figure 8]. Similarly, decreased mitochondrial fusion, particularly due to reduced mitofusin 2, can exacerbate myocardial injury during diabetic myocardial I/R via the cGAS–STING signaling pathway.^[169] Preserving mitochondrial function and inhibiting the cGAS–STING activation could attenuate DCM progression.^[170,171] Pyroptosis, typically mediated by inflammasome activation, is implicated in DCM through signaling pathways such as the NF- κ B, mtROS, and adenosine 5'-monophosphate-activated protein kinase^[172] [Figure 8]. Free FAs can cause NLRP3 inflammasome activation and pyroptosis in cardiomyocytes via a cGAS–STING-dependent signaling pathway, resulting in mitochondrial dynamics and structural and functional cardiac impairments in DCM^[168] [Figure 8]. These findings collectively highlight that direct inhibition of the cGAS–STING signaling pathway or upstream signaling axes may represent an effective therapeutic strategy for DCM [Figure 8].

Overall, recent studies have increasingly highlighted the role of the cGAS–STING pathway in cardiovascular diseases, including MI, cardiomyopathy, and HF. Dysregulated activation of the cGAS–STING pathway is associated with inflammatory responses and abnormalities in cellular homeostasis. Targeting cGAS–STING signaling has shown promise in mitigating inflammatory infiltration, adverse remodeling, and cardiac dysfunction, highlighting its potential as a novel therapeutic strategy in cardiovascular pathology.

cGAS–STING signaling pathway in blood disorders

Leukemia

Leukemia is defined by the presence of circulating malignant white blood cells. It is clinically classified into four primary subtypes: acute myeloid leukemia (AML), acute lymphoblastic leukemia/lymphoma (ALL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and chronic myeloid leukemia (CML).^[173] During hematopoietic stem cell transplantation in murine myeloid leukemia models, leukemia cells secrete dsDNA via extracellular vesicles, which impairs the hematopoietic functions of donor cells. Cytoplasmic DNA accumulation activates the cGAS–STING signaling pathway, reducing leukemia cell viability through ROS generation^[174] [Figure 3]. Bone marrow macrophages suppress leukemia expansion via LC3-associated phagocytosis, in which mtDNA activates STING, releasing inflammatory signals that promote phagocytosis and restrict leukemic cell proliferation.^[175,176] Systemic immunotherapy via a lipid-based nanoparticle platform carrying Mn²⁺ and the STING agonist c-di-AMP (CDA) exhibited robust antitumor efficacy in a disseminated AML mouse model.^[177] Controversially, recent studies have demonstrated that negative regulation of STING signaling can inhibit leukemia progression.^[178] Surfeit 4, a multipass ER transmembrane protein involved in the ER–Golgi compartment, is frequently amplified and highly expressed in leukemic cells. Surfeit 4 suppresses myeloid differentiation and inhibits leukemia cell death by negatively regulating the STING–TBK1–STAT6 axis.^[178]

AML with tumor protein p53 (TP53) mutation is associated with a highly lethal phenotype and poor prognosis.^[179] In TP53-mutated AML, histone modifications and polyploidy activate the cGAS–STING signaling pathway, leading to cytokine and chemokine secretion and subsequent activation of macrophages and T cells upon coculture with AML cells.^[179,180] In TP53-mutant blood cancers, STING agonists induce the expression of pro-apoptotic BH3-only protein in a p53-independent manner, leading to the death of AML cells.^[181] Somatic loss-of-function mutations in the dioxygenase ten-eleven translocation-2 gene are frequent in AML patients. STING inhibition specifically reduces the proliferation of leukemia cells from dioxygenase ten-eleven translocation-2-mutated individuals in patient-derived xenograft models.^[182] AML patients harboring a RUNX1:RUNX1T1 fusion present an approximately 50% relapse rate. Kasumi-1 cells expressing this fusion protein exhibit increased DNA damage signals, triggering cGAS–STING signaling pathway activation.

STING deletion in a mouse primary RUNX1:RUNX1T1 leukemia model reduces leukemogenesis and extends survival.^[183] In addition, promyelocytic leukemia (PML) expresses SASP in senescent cells via the CCF–cGAS–STING–TBK1–NF- κ B signaling pathway^[184] [Figure 3]. In a *Sting*-deficient CLL mouse model, *Sting*-deficient CLL cells are more responsive to B-cell receptor activation, and both human and mouse malignant CLL cells downregulate STING to increase B-cell receptor signaling for survival.^[185] Collectively, these studies indicate that the cGAS–STING signaling pathway plays various roles in different types of leukemia and that targeting STING may be beneficial for enhancing the antitumor effects of leukemia immunotherapy.

Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent form of non-Hodgkin lymphoma globally, with approximately 150,000 new cases reported annually.^[186] Genomic instability is a significant driver of cancer progression. Extrachromosomal circular DNAs induced by DNA damage promote oncogenesis in DLBCL by activating STING signaling in a cGAS-independent manner.^[187] Inhibition of STING and STAT3 signaling pathways hinders the proliferation of Epstein–Barr virus-infected B cells and the transformation of lymphoblastoid cell lines.^[188] However, emerging evidence suggests that cGAS–STING activation may enhance the efficacy of radiochemotherapy in DLBCL.^[189–191] Specifically, bendamustine-rituximab therapy has been shown to activate the cGAS–STING signaling pathway, resulting in the release of inflammatory cytokines, upregulation of major histocompatibility complex molecules, and the creation of an immunologically “hot” TME. This cascade of events ultimately induces pyroptosis in DLBCL cells.^[189] Epigenetic priming has also been reported to increase the efficacy of salvage chemotherapy in DLBCL by activating the cGAS–STING signaling pathway via endogenous retroviruses.^[190] Furthermore, the STING agonist DMXAA has been shown to increase the efficacy of PD-L1 inhibitors in DLBCL.^[191]

Peripheral T-cell lymphoma (PTCL) represents a heterogeneous group of mature T-cell neoplasms. High expression of the cGAS–STING signaling pathway is closely linked to PTCL proliferation. Specifically, inhibition of cGAS suppresses tumor growth and disrupts DNA damage repair mechanisms^[192] [Figure 3]. Notably, STING expression is predominantly confined to T- and NK-cell lymphomas and is downregulated in B-cell non-Hodgkin lymphoma.^[193] Targeting cytidine triphosphate synthase 1 has been demonstrated to induce immune responses via the cGAS–STING signaling pathway in mantle cell lymphoma, which is pivotal for inhibiting tumor growth in mantle cell lymphoma patients.^[194]

Multiple myeloma (MM)

MM is a neoplastic disorder of the hematopoietic system characterized by the uncontrolled proliferation of neoplastic plasma cells within the bone marrow. This

proliferation results in skeletal destruction, renal impairment, anemia, and hypercalcemia.^[195] Myeloma-derived mtDNA alters the bone marrow niche by activating the cGAS–STING signaling pathway in tumor-associated macrophages, thereby promoting disease progression.^[196] In MM, cGAS–STING signaling pathway activation induces cell death through the IRF3–NOXA–BAX/BCL-2 antagonist/killer 1 (BAK) axis and triggers M1 macrophage polarization^[197] [Figure 3]. In addition, viral infections significantly contribute to morbidity and mortality in MM patients. Exosomes derived from MM cells are enriched in microRNAs that are transferred to host monocytes/macrophages, where they suppress the cGAS–STING signaling pathway, reduce IFN-I production, and impair the innate immune response to DNA viruses.^[198]

The standard first-line therapy for MM patients typically includes a combination of an injectable proteasome inhibitor (e.g., bortezomib), an oral immunomodulatory drug (e.g., lenalidomide), and dexamethasone.^[195] Bortezomib enhances the immunogenicity of MM cells by activating the cGAS–STING signaling pathway and inducing IFN-Is [Figure 3]. The coadministration of STING agonists with bortezomib elicits a robust tumor-specific immune response and improves clinical outcomes in MM patients.^[199] The DNA-dependent protein kinase catalytic subunit (DNA-PKcs) is a DNA damage repair factor. Inhibition of DNA-PKcs enhances the anti-MM effects of doxorubicin by activating the cGAS–STING signaling pathway.^[197] Collectively, these findings suggest that the combination of STING agonists with chemotherapeutic agents may offer therapeutic advantages for MM patients.

In summary, STING agonists demonstrate significant antitumor efficacy in hematologic malignancies. However, these cancers frequently harbor genetic mutations, and the cGAS–STING signaling pathway has divergent effects depending on the mutation sites. Therefore, future research targeting the cGAS–STING signaling pathway should focus on specific malignancy subtypes to achieve precision medicine.

cGAS–STING signaling pathway in respiratory system diseases

Lung cancer

In lung cancer, particularly metastatic lung adenocarcinoma, STING functions as a checkpoint to suppress the outgrowth of reawakened dormant cancer cells [Figure 3]. STING activity increases as metastatic progenitors exit dormancy, but its function can be suppressed through hypermethylation of regulatory regions or chromatin repression. Encouragingly, the activation of STING via agonists has demonstrated promise in eliminating dormant metastases and preventing disease relapse via T-cell- and NK cell-mediated mechanisms in lung adenocarcinoma^[200] [Figure 3]. However, challenges emerge in KRAS-LKB1-mutant lung cancers, where intrinsic mitochondrial dysfunction silences STING, resulting in T-cell exclusion and resistance to PD-1/PD-L1 blockade. These cancers further avoid downstream STING and STAT1

activation by minimizing 2'3'-cGAMP accumulation. Notably, combining epigenetic reactivation of STING with transient monopolar spindle 1 kinase inhibition restores STING activity, enhances T-cell infiltration, and improves anti-PD-1 efficacy *in vivo*.^[201] These findings underscore STING as a pivotal target for overcoming immune evasion and improving therapeutic outcomes in lung cancer.

Lung fibrosis

In addition to its role in cancer, STING also significantly contributes to lung fibrosis through its involvement in the STING–PERK–eIF2 α axis, a noncanonical cGAS–STING signaling pathway [Figure 3]. This mechanism links innate DNA sensing to cellular translation. Upon cGAMP binding, STING activates PERK in the ER, leading to eIF2 α phosphorylation and a shift toward an inflammatory translation program [Figure 3]. The STING–PERK–eIF2 α signaling pathway is critical in the development of lung fibrosis, and its targeting has been shown to attenuate lung fibrosis.^[36] Similarly, in silica-induced lung inflammation and fibrosis, STING is activated by self-dsDNA released in the lungs following cell death. Degradation of extracellular dsDNA by DNase I inhibits STING activation and downstream IFN-I responses, highlighting DNase I as a potential therapy. Consistently, in silicosis patients, increased circulating dsDNA and STING activation are associated with inflammatory markers such as CXCL10, further supporting the role of STING-mediated DNA sensing in silica-induced lung inflammation.^[202]

Asthma

STING also contributes to the pathogenesis of severe asthma by driving neutrophilic lung inflammation. The activation of STING exacerbates airway hyperresponsiveness through cell death via PANoptosis, extracellular dsDNA release, and the activation of DNA sensors [Figure 3]. In asthma models, STING agonists such as diABZI enhance neutrophil recruitment, airway hyperresponsiveness, and a mixed Th1/Th2 inflammatory response. These effects include epithelial barrier damage, tight junction downregulation, and increased release of inflammatory markers, mirroring features of severe asthma.^[203]

In summary, STING is a critical mediator of immune responses in respiratory diseases, including lung cancer, fibrosis, and asthma. Its activation or dysregulation underpins key pathological processes, making it a promising target for future therapeutic strategies.

cGAS–STING signaling pathway in urinary system diseases

Acute kidney injury (AKI)

In AKI, mitochondrial dysfunction and subsequent activation of the cGAS–STING signaling pathway drive inflammation and kidney damage.^[204] Cisplatin-induced AKI leads to mtDNA leakage into the cytosol through BCL2-associated X (BAX) pores in the mitochondrial outer membrane, thereby triggering STING activation

and inflammatory responses. Studies in STING-deficient mice and tubular cell models have shown reduced inflammation and improved outcomes, emphasizing the central role of the STING signaling pathway^[205] [Figure 3]. Furthermore, elevated plasma mtDNA in patients receiving platinum-based chemotherapy suggests that STING activation contributes to AKI. Therapeutically, the STING antagonist H151 has demonstrated significant efficacy in improving renal function, reducing tubular apoptosis, and alleviating inflammation and mitochondrial injury in cisplatin-induced AKI models, highlighting its potential as a treatment option^[206] [Figure 3].

Chronic kidney disease (CKD)

In addition to AKI, STING also contributes to kidney fibrosis, a hallmark of CKD. In a *Tfam* knockout mouse model, mitochondrial defects caused mispackaging of mtDNA, leading to its cytosolic translocation and subsequent activation of the cGAS–STING signaling pathway. This activation results in cytokine expression, immune cell recruitment, and fibrosis progression [Figure 3]. Importantly, ablation of *Sting* significantly reduces fibrosis, further supporting its therapeutic potential in CKD.^[207]

Bladder cancer

In bladder cancer, the cGAS–STING signaling pathway shapes the TME by driving the differentiation of a specific subpopulation of cancer-associated fibroblasts (CAFs) characterized by SLC14A1 overexpression. These SLC14A1⁺ CAFs are induced by interferon signaling via STING activation in tumor cells. Mechanically, these SLC14A1⁺ CAFs promote bladder cancer cell stemness through the wntless-type MMTV integration site family member 5A paracrine signaling pathway, leading to poor outcomes and resistance to chemotherapy and immunotherapy^[208] [Figure 3].

In summary, the cGAS–STING signaling pathway plays diverse yet interconnected roles in urinary and renal diseases, mediating inflammation and mitochondrial dysfunction in AKI, driving fibrosis in CKD, and modulating the TME in bladder cancer. These findings establish STING as a promising target for therapeutic interventions across these conditions.

cGAS–STING signaling pathway in reproductive system diseases

Endometriosis

Endometriosis refers to a gynecological condition characterized by the presence of endometrial tissues (epithelium and/or stroma) outside the uterus.^[209] Immunological, inflammatory, proangiogenic, and endocrine factors contribute to endometrial cell survival and proliferation outside the uterus.^[210] Recent data have demonstrated elevated cGAS–STING expression and autophagy activity in the ectopic endometria of humans and mice compared with normal and eutopic endometria.^[211] The expression

of STING reflects the chronic inflammatory state within the tissue microenvironment, facilitating the establishment and maintenance of ectopic lesions.^[212,213] As crucial immune cells, macrophages drive endometriosis development by sustaining a chronic pelvic inflammatory state and promoting ectopic endometriotic lesion proliferation.^[214] Macrophage activation, associated with the cGAS–STING signaling pathway, contributes to ovarian dysfunction through inflammatory responses, apoptosis, and cellular senescence.^[215] These findings may provide a theoretical basis for understanding infertility associated with ovarian endometriosis. In addition, autophagy activity and human endometrial stromal cell motility increased in a lentivirus-based model of *STING* overexpression^[211] [Figure 3]. These findings collectively indicate that the cGAS–STING signaling pathway can enhance autophagy, thereby promoting the migration and invasion of ectopic endometrial cells. The application of STING inhibitors may attenuate downstream development and reduce endometriosis lesions.^[211,215]

Adenomyosis

Adenomyosis is characterized by the growth of endometrial epithelial cells and stromal fibroblasts into the myometrium and was initially considered a variant of endometriosis. Hypoxia, inflammation, immune cell infiltration, and platelet activation can promote the differentiation of Schwann cells at the endometrial–myometrial interface into endometrial cells, thus inducing adenomyosis.^[216] Hypoxia can lead to mitochondrial damage and mitophagy, processes implicated in various diseases, including adenomyosis.^[217,218] Elevated mtDNA levels, resulting from mitochondrial damage, are observed in hypoxic endometrial stromal cells and can activate the cGAS–STING signaling pathway. Notably, inhibiting mtDNA replication can reverse hypoxia-induced STING expression. STING activation promotes an inflammatory state by producing the downstream cytokines IL-6 and TNF- α in adenomyosis and is correlated with abnormal cell proliferation and migration under hypoxic conditions [Figure 3].^[219] Furthermore, the expression of TBK-1 and TNF- α in adenomyotic lesion tissue is positively correlated with the severity of dysmenorrhea in patients, providing robust clinical evidence supporting the involvement of this signaling pathway in adenomyosis.^[220]

Reproductive cancer

Ovarian cancer is the most fatal gynecological malignancy, with a global 5-year survival rate of 30–40%.^[221] Epithelial ovarian cancer is the most common subtype, with high-grade serous ovarian cancer being the primary contributor to patient mortality. The STING signaling pathway promotes resistance by modulating the cancer-immunity cycle^[222] [Figure 3]. In ovarian cancer, the cGAS–STING deficiency impairs STING-dependent DNA sensing, a key immune evasion mechanism,^[223,224] potentially driven by elevated USP35 deubiquitinase expression.^[225] Furthermore, STING expression is correlated with tumor histology and clinical stage.^[224,226] Numerous studies have proposed that modulating the

STING signaling pathway may provide new insights into ovarian cancer chemotherapies, including strategies to overcome drug resistance. Despite these interventions, ovarian cancer is characterized by a high recurrence rate and drug resistance, prompting the integration of novel therapies such as poly ADP-ribose polymerase (PARP) inhibitors.^[227] While the STING signaling pathway activation may elucidate the antitumor mechanisms of PARP inhibitors^[228] [Figure 3], resistance is increasingly prevalent and associated with M2-like polarization of tumor-associated macrophages in the TME. STING agonists can alter myeloid cell function, potentially overcoming this resistance.^[229] However, a recent study revealed that cisplatin resistance in ovarian cancer may be associated with cGAS–STING signaling pathway activation in CAFs, which can be reversed with STING inhibitors.^[230] Hence, the role of STING as either a tumor suppressor or promoter remains context-dependent, necessitating caution in the therapeutic use of STING agonists for ovarian cancer.^[231]

In summary, emerging evidence indicates a significant association between the cGAS–STING pathway and reproductive disorders, with its roles varying across different pathological contexts. Aberrant activation of the cGAS–STING pathway is associated with an excessive inflammatory state in reproductive dysfunction. Conversely, this pathway is crucial for promoting antitumor immunity. A deeper understanding of these signaling pathways may provide new insights into unexplained reproductive disorders, such as endometriosis and adenomyosis, while also addressing challenges related to tumor drug resistance.

cGAS–STING signaling pathway in autoimmune diseases

Systemic lupus erythematosus (SLE)

SLE is a multisystemic autoimmune disease characterized by the production of antibodies against nuclear antigens, immune complex deposition, and chronic inflammation in target organs such as the skin, joints, and kidneys.^[232] The pathogenesis of SLE is associated with dysregulated activation of the IFN-I signaling pathway and the presence of an IFN-stimulated gene signature^[233] [Figure 3]. The IFN response is initiated by the engagement of oxidized DNA with the cytosolic DNA-sensing complex cGAS–STING.^[234] A subset of SLE patients exhibits impaired function of hypoxia-inducible factor-regulated metabolic and proteasomal signaling pathways, leading to the accumulation of mitochondria-containing red blood cells (Mito⁺ RBCs). When phagocytosed by macrophages, these Mito⁺ RBCs trigger cGAS–STING-dependent inflammation.^[235] Monocytes co-produce IFN-I and mature IL-1 β in response to opsonized Mito⁺ RBCs^[236] [Figure 3]. The DNA repair enzyme 8-oxoguanine glycosylase 1, which corrects 8-oxo-2'-deoxyguanosine, modulates IFN- β expression via the cGAS–STING signaling pathway in a pristane-induced SLE mouse model.^[234] These findings highlight the critical role of the cGAS–STING signaling axis in SLE pathogenesis and its potential as a therapeutic target for autoinflammation.

Deficiency or pharmacological inhibition of STING has been shown to ameliorate SLE in murine models.^[237,238] Peripheral blood mononuclear cells (PBMCs) from SLE patients exhibit increased phosphorylation of IRF8 and enhanced STING activity.^[239] The RNF115 protein can exacerbate STING-mediated inflammation and autoimmunity, and this effect can be mitigated by the RNF115 inhibitor disulfiram. Downregulation of RNF115 disrupts STING oligomerization and Golgi localization in various cell types, resulting in reduced expression of IFN- α , IFN- γ , and proinflammatory cytokines in PBMCs from SLE patients^[240] [Figure 3]. Conversely, a study suggested that a deficiency in both cGAS and STING does not protect mice from tetramethylpentadecane-induced SLE and is associated with increased autoantibody production and proteinuria levels compared with those in cGAS- and STING-sufficient mice.^[241] Thus, further investigation is necessary to clarify the mechanisms by which STING contributes to SLE and to assess the potential of STING as a therapeutic target in SLE and associated autoimmune diseases.

Rheumatoid arthritis (RA)

RA is a chronic systemic autoimmune disorder predominantly affecting joints and periarticular soft tissues.^[242] In a mouse model of inflammatory arthritis, cGAS deficiency has been shown to block IFN responses, reduce inflammatory cell infiltration, and alleviate joint swelling^[243] [Figure 3]. Similarly, inhibiting the STING signaling pathway ameliorates joint damage in mouse models of dsDNA-induced and collagen-induced arthritis.^[244] Moreover, several studies have demonstrated that TBK1 recruitment to STING mediates autoinflammatory arthritis independently of IFN-I signaling^[245,246] [Figure 3].

The cGAS-STING signaling pathway is central to regulating the aggressive behavior of rheumatoid synovial tissues. Fibroblast-like synoviocytes are key pathogenic players in RA. Fibroblast-like synoviocytes exhibit increased cGAS expression upon TNF- α stimulation, underscoring the role of TNF in RA progression via the cGAS-STING axis.^[243] In addition, increased expression of fat mass and obesity-associated protein (FTO) in RA synovial cells promotes their proliferation and migration while inhibiting senescence and apoptosis. The FTO-CMPK2 signaling pathway is essential for modulating synovial inflammation through the mtDNA-mediated cGAS-STING signaling pathway, thereby influencing chondrocyte homeostasis.^[247] DNA polymerase β (Pol β), a key enzyme in base excision repair, is significantly downregulated in PBMCs from active RA patients and collagen-induced arthritis mice. Pol β deficiency leads to DNA damage accumulation and cytosolic dsDNA leakage, activating the cGAS-STING-NF- κ B signaling pathway and upregulating NLRP3, IL-1 β , and IL-18 expression, ultimately inducing macrophage pyroptosis^[248] [Figure 3]. These findings suggest that Pol β may serve as a potential therapeutic target for the prevention and treatment of RA and related autoimmune diseases.

In summary, the cGAS-STING signaling pathway, which detects mislocated self-DNA to trigger pathogenic IFN-I and cytokine production, is a crucial driver of inflammation

in autoimmune diseases such as SLE and RA. Despite the therapeutic potential of STING inhibition demonstrated in numerous mouse models of autoimmune diseases, therapeutic strategies must precisely target pathological signaling while preserving essential host defenses.

cGAS-STING signaling pathway in pathogen infection

The cGAS-STING signaling pathway is crucial in initiating host defense against microbial infections [Figure 3]. In *Drosophila melanogaster*, two cGAS-like receptors produce 3'2'-cGAMP and 2'3'-cGAMP to activate STING. Recent studies have shown that various CDNs, including 2'3'-c-di-GMP, are produced in a cGLR-dependent manner in response to viral infection [Figure 3]. Notably, 2'3'-c-di-GMP is a more potent STING agonist than cGAMP in *D. melanogaster* and induces a robust antiviral transcriptional response in *D. serrata*.^[249] STING serves as the first line of defense against infections, primarily through IFN-I production.^[250,251] However, for successful viral infection, immune evasion mechanisms must be used. Upon DNA virus infection, myb-like, swirm and mpn domain 1 (MYSM1) expression is induced. MYSM1 subsequently interacts with STING and cleaves K63-linked ubiquitinated STING to suppress cGAS-STING signaling.^[252] In addition, the oncogenes E7 from human papillomavirus 18 and E1A from adenovirus inhibit the cGAS-STING signaling pathway.^[253] The phase separation of cGAS-DNA is essential for the antiviral innate immune response. Viral tegument proteins restrict cGAS-DNA phase separation to overcome innate immunity.^[254] Virus-like particles induce cGAS liquid-phase condensation and activate STING signaling, leading to the production of inflammatory cytokines and enhanced antitumor immunity.^[255] These findings suggest that viruses suppress the cGAS-STING signaling pathway for immune evasion [Figure 3].

Herpes simplex virus 1 (HSV-1) effectively establishes acute and latent human infections by antagonizing host antiviral innate immune responses. Upon infection, viral capsids are transported along the cytoskeleton within the cytoplasm, followed by the injection of the viral genome into the nucleus via the nuclear pore complex. DNA sensor-mediated innate immune signaling pathways are important in restricting HSV-1 infection.^[256,257] The HSV-1 γ (1)34.5 protein directly interacts with STING to prevent its transport from the ER to the Golgi apparatus, thereby inhibiting STING activation and downstream antiviral signaling pathways.^[257] Preventing STING degradation enhances IFN production, reduces viral replication, and diminishes cellular infiltration.^[251]

The cGAS-STING signaling pathway is essential for IFN-I induction during varicella-zoster virus (VZV) infection, and the recognition of VZV by cGAS inhibits viral replication^[258,259] [Figure 3]. The VZV tegument protein ORF9 acts as a cGAS antagonist, reducing IFN-I responses.^[258] VZV glycoprotein E facilitates PINK1/Parkin-mediated mitophagy to evade STING-mediated antiviral innate immunity.^[259] In human cytomegalovirus (HCMV), the HCMV-encoded UL37 exon-1 protein inhibits the cGAS-STING signaling pathway through

direct interaction with TBK1.^[260] Despite its antiapoptotic function in enhancing immune signaling, the immunosuppressive activity of the HCMV-encoded UL37 exon-1 protein mitigates this potential side effect.^[260] Moreover, cytomegalovirus infections can be effectively controlled by STING-mediated immune responses in hematopoietic and stromal cells.^[250]

RNA viruses, such as parainfluenza virus and rhinovirus, are major pathogens responsible for respiratory infections. STING activation has been shown to exert significant antiviral effects against parainfluenza virus 3 and rhinovirus 16^[261] [Figure 3]. Dengue virus, an RNA virus without a DNA stage, manipulates cGAS–STING-mediated innate immunity through proteolytic degradation of STING. The overexpression of cGAS or DNA virus reactivation in cells leads to enhanced STING cleavage in neighboring cells containing dengue virus protease.^[262] During foot-and-mouth disease virus infection in swine cells, the viral proteases leader and 3C protease cleave cGAS, attenuating the cGAS–STING-dependent antiviral response.^[263] In the pseudorabies virus model, tegument protein US2 interacts with STING, recruiting the E3 ubiquitin ligase TRIM21 to facilitate K48-linked ubiquitination and subsequent STING degradation.^[264] Collectively, these findings indicate that viruses can evade innate immunity by inhibiting cGAS–STING activity, suggesting that STING agonists may serve as potential targets for antiviral therapeutics.

The cGAS–STING signaling pathway constitutes a critical innate immune defense mechanism against pathogens, inducing IFN-I production and antiviral responses upon cytosolic DNA sensing. However, diverse viruses (e.g., HSV-1, VZV, HCMV, dengue virus, foot-and-mouth disease virus, and pseudorabies virus) use species-specific strategies to evade or suppress the cGAS–STING signaling pathway. Mechanisms include cleaving cGAS or STING, blocking STING trafficking, disrupting phase separation, or exploiting host processes such as mitophagy. This pervasive viral evasion underscores the fundamental role of the cGAS–STING signaling pathway while highlighting challenges for its therapeutic exploitation.

cGAS–STING signaling pathway in aging

Aging is a complex, natural, and irreversible biological process. Cellular senescence, a stable state of proliferative arrest, is a major contributor to organismal aging.^[265] It is characterized by permanent cell cycle arrest, changes in the cellular secretome, imbalances in macromolecules, and alterations in organelle structure and function.^[266] One of the key hallmarks of senescent cells is the SASP, which involves various factors that exert autocrine and paracrine effects, reshaping the local microenvironment and promoting further senescence. SASP is a form of molecular inflammation, and chronic overproduction of these factors contributes to chronic low-grade inflammation known as inflammaging.^[267] The cGAS–STING signaling pathway may serve as a central mediator linking age-induced cellular damage and SASP activation through the IFN signaling pathway^[268] [Figure 3]. DNA damage, a significant trigger for the cGAS–STING signaling, may be associated with various molecular mechanisms of

senescence, including genomic instability, epigenetic alterations, and mitochondrial dysfunction.^[269]

The SASP is predominantly driven by CCFs in senescent cells.^[270] These micronuclei-like structures, generated via nuclear membrane blebbing, contain genomic DNA and act as upstream activators of cGAS.^[271] The topoisomerase 1-DNA covalent cleavage complex may enhance cGAS binding to CCFs, a crucial interaction for cGAS-mediated DNA sensing and subsequent SASP activation during the aging process^[272] [Figure 3]. Key challenges lie in elucidating the mechanisms of CCF formation and ectopic DNA accumulation, which trigger sensor activation during senescence. Loss of lamin B1 in the nuclear lamina can compromise the integrity of the nuclear membrane. In mouse embryonic fibroblasts, siRNA-mediated knockdown of lamin B1 led to CCF formation and recognition by cGAS.^[273,274] In addition, decreased activity of mechanosignaling genes yes-associated protein and tafazzin in stromal and contractile cells, mediated through Lamin B1 and actin-related protein 2, disrupts nuclear membrane integrity and facilitates SASP via the cGAS–STING signaling pathway.^[275] Two major deoxyribonucleases responsible for cytoplasmic DNA degradation, deoxyribonuclease 2 and three prime repair exonuclease 1 (TREX1), are both downregulated during senescence. In fact, cytoplasmic DNA accumulation in the absence of functional DNase can also facilitate the DNA damage–cGAS–SASP axis in senescent cells.^[276,277]

Loss of heterochromatin during aging can promote retrotransposon derepression in genomic instability, another potential mechanism of cGAS–STING activation.^[278] LINE-1s elements, the most abundant retrotransposons, play crucial roles in senescence and inflammaging via the cGAS–STING signaling pathway. In aging mice, increased LINE-1 activity results in cDNA accumulation, thereby eliciting a type I interferon response via the cGAS–STING signaling pathway.^[279] Modulating LINE-1 activity, such as through brain and muscle ARNT-like 1 (BMAL1, which inhibits the LINE-1–cGAS–SASP cascade) or paired box 5 (PAX5, which promotes LINE-1 activation), can influence cellular senescence^[280,281] [Figure 3]. Interestingly, nuclear cGAS can suppress LINE-1s by affecting open reading frame 2 protein stability following DNA damage, highlighting the dual functions of cGAS in the nucleus and cytoplasm during aging, as well as the multifaceted regulation of LINE-1 activity.^[282]

Mitochondrial dysfunction is also implicated in aging. The release of mtDNA from damaged mitochondria is a significant source of cytoplasmic DNA, activating the cGAS–STING signaling pathway. In microglia, mitochondrial dysfunction drives aging-related innate immune activation and neurodegeneration via the cGAS–STING signaling pathway, with TNF exerting downstream neurotoxic effects.^[283] Mitochondrial outer membrane permeability (MOMP) is a key event in mtDNA leakage, which occurs in a BAK-dependent manner.^[284] During aging, the formation of BAX and BAK pores also induces a phenomenon called “miMOMP”, where a small fraction of mitochondria exhibits increased MOMP and activates the cGAS–STING signaling pathway during

aging.^[285] However, unlike MOMP, which typically occurs during cellular apoptosis, miMOMP does not affect cyclin-dependent kinase inhibitors, thus mediating the progression of cellular senescence. Overall, impaired mitochondrial integrity drives cGAS–STING activation, contributing to inflammaging, but this process is mitigated by mitophagy.^[286,287] With increasing age, the increase in mitophagy in multiple organs of mice may be a reaction to cGAS–STING activation. Drug-induced mitophagy has improved neurological and visual functions in aged mice, offering new insights for developing therapeutic strategies against aging-related diseases.^[287]

In summary, cytosolic DNA accumulation recognized by cGAS can induce the SASP and drive inflammaging. Various upstream factors can modulate this process, including the compromised nuclear membrane integrity, DNase downregulation, retrotransposon derepression, and mitochondrial dysfunction. Serving as a pivotal connection between DNA damage and inflammation in senescence, the cGAS–STING pathway presents diverse therapeutic targets for aging-related diseases.

cGAS–STING signaling pathway in other diseases

Ophthalmic diseases

The immune-inflammatory response critically contributes to multifactorial ocular surface diseases such as dry eye, characterized by tear film hyperosmolarity, oxidative stress, and epithelial cell damage.^[288] Mitochondrial homeostasis maintains corneal epithelial cell stability to defend against environmental stresses. Recently, researchers have provided evidence for the activation of the cGAS–STING signaling pathway in dry eye disease across both environmental and non-environmental models^[289,290] [Figure 3], potentially initiated by mitochondrial permeability transition pore opening and the subsequent mtDNA leakage into the cytoplasm. Hyperosmotic conditions also induce ROS production, primarily due to mitochondrial dysfunction, exacerbating oxidative mtDNA damage.^[291,292] The cGAS–STING signaling pathway responds by upregulating NF- κ B and IFN- β ^[293] [Figure 3], with oxidized mtDNA detected by cGAS implicated as a trigger.^[294] These results indicate mitochondrial impairment is a key precursor for cGAS–STING activation in dry eye disease.^[295]

Glaucoma is characterized by retinal ganglion cell (RGC) degeneration and neuroinflammation of retinal glial cells.^[296] A recent study^[297] indicated that the cGAS–STING signaling pathway is activated within the microglia of RGCs at the early axonal debris stage, coinciding with mitochondrial dysfunction. Neuroinflammation-induced RGC ischemia may initiate the sensing process and exacerbate retinal damage by amplifying the inflammatory response.^[298] Furthermore, microglial cGAS–STING activation contributes to macroglial reactivity, providing novel insights into the interactions between different glial cells in glaucoma.^[299] Strategies targeting cGAS–STING–IFN signaling, including TBK1 inhibitors, IFNAR1 antibodies, and genetic deletion of STING, are beneficial

for protecting RGC cells and preserving visual quality [Figure 3].

Ischemia, pathological angiogenesis, photoreceptor degeneration, and inflammation are common events in various retinopathies, such as diabetic retinopathy, age-related macular degeneration, and retinopathy of prematurity. An increasing number of studies are exploring the activation of the cGAS–STING signaling pathway in retinal damage and the corresponding therapeutic options. The cGAS–STING signaling pathway contributes to the activation of retinal myeloid cells, including microglia and macrophages, which can further promote neovascularization in the retina.^[300–302] The preservation of mitochondrial function has been shown to reduce retinal damage,^[301,303] reinforcing the central roles of mitochondria and the cGAS–STING signaling pathway in retinopathy. Modulating macrophage polarization to block this inflammatory response and alleviate angiogenesis may represent alternative options for anti-VEGF therapies.^[300] Bromodomain and extraterminal domain (BET) protein inhibitors, such as dBET6 and JQ1,^[304,305] can also attenuate cGAS–STING signaling pathway activation and protect photoreceptor cells.

Ocular diseases are closely associated with inflammation. The activation of the cGAS–STING, a key inflammatory signaling pathway, contributes to the progression of various ocular diseases, including dry eye disease, glaucoma, and retinal diseases. Targeting the excessive inflammatory responses mediated by the cGAS–STING pathway may present a novel therapeutic strategy for ocular diseases.

Chronic rhinosinusitis (CRS)

CRS is a common upper airway inflammatory disease with two major phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps. Eosinophilic CRS (eCRS) is driven by type 2 immune response and is characterized by eosinophil infiltration.^[306] Pattern-recognition receptors such as Toll-like receptors are activated in the epithelial innate immune response, providing antiviral and antibacterial functions.^[307] However, the role of the cGAS–STING signaling pathway in CRS, especially eCRS, requires more in-depth research. The STING signaling pathway exerts a dual role in modulating the innate immune response and type 2 inflammation in CRSwNP patients.^[308] In the eosinophilic subtype, reduced STING expression and subsequent decreased IFN-I production indicate impaired antiviral resistance and exacerbated inflammation [Figure 3]. This observed reduction in STING expression may be attributed to the activity of IL-4 and IL-13 in type 2 inflammation.^[308] Researchers have further reported that IL-13 is activated through suppressor of cytokine signaling 1 following defective STING expression in eosinophilic CRSwNP.^[309] Given its involvement in both innate and type 2 immune responses, the STING pathway represents a promising therapeutic target for eosinophilic CRSwNP, a clinically challenging and severe subtype, despite the need for further research.

Oral diseases

The cGAS–STING signaling pathway is correlated with oral cancer and inflammatory diseases, offering new insights for therapeutic interventions. Oral squamous cell carcinoma (OSCC) is a cancer that originates from the epithelium of the oral mucosa. It is classified as a type of head and neck squamous cell carcinoma (HNSCC), which ranks as the sixth most common cancer worldwide.^[310] Most patients develop chemotherapy resistance, leading to a poor prognosis and posing significant challenges to treatment.^[311] A recent study suggested targeting casein kinase 2-interacting protein 1 (CKIP-1) may be an effective therapeutic strategy. Silencing CKIP-1 can effectively inhibit various malignant behaviors of OSCC tumors by influencing mitochondrial homeostasis and activating the cGAS–STING signaling pathway.^[312] Another study indicated that STING agonists can positively enhance both local and systemic antitumor immune effects^[313] [Figure 3]. Intratumoral injection of STING agonists has been shown to augment checkpoint blockade in HNSCC. Specifically, in preclinical models of HPV-positive oral tumors, the STING agonist ML-RR-CDA can increase PD-1/PD-L1 expression, thereby improving the therapeutic effects of systemic α -PD-1. Apical periodontitis is a common destructive inflammatory oral disease caused primarily by microbial infection. During the dynamic regulation of immune responses, the innate immune system initiates the process through various pattern recognition receptors, including the cGAS.^[314,315] Apical periodontitis is characterized by progressive alveolar bone disruption,^[316] a process partly mediated by activated

STING signaling [Figure 3]. STING inhibitors might provide an effective nonsurgical treatment option by inhibiting osteoclast differentiation and bone resorption, thus preventing bone loss.^[317]

Potential Therapeutic Targets and Clinical Trials

The role of the cGAS–STING signaling pathway in the pathogenesis of human diseases has been discussed above. Based on these studies, researchers have developed a series of agonists and inhibitors that target the cGAS–STING signaling pathway. Here, we summarize the known agonists and inhibitors of the cGAS–STING signaling pathway [Tables 1 and 2] and compile relevant clinical trials [Table 3].

Agonists and inhibitors of the cGAS–STING signaling pathway

Agonists and inhibitors of cGAS

Agonists of cGAS

Metal ions are essential for normal cellular activities. Studies have shown that Mn^{2+} alone can directly activate cGAS in a dsDNA-independent manner, driving the unconventional catalytic synthesis of 2'3'-cGAMP.^[318,319] [Table 1]. By activating the cGAS–STING–NLRP3 axis, Mn^{2+} enhances antigen uptake, presentation, and germinal center formation, robustly amplifying immune responses.^[320] Currently, multiple therapeutic strategies have been developed based

Table 1: Agonists and inhibitors of cGAS.

Type	Name	Mechanism	References
Agonist	Mn^{2+}	Strengthens cGAS sensitivity to dsDNA	[319]
Agonist	Zn^{2+}	Promotes cGAS phase transition	[325]
Agonist	β -Arrestin 2	Enhances the cGAS DNA-binding ability	[328]
Agonist	Chitosan	Stimulates the intracellular DNA release	[330]
Inhibitor	Suramin, X6	Shields cGAS DNA-binding sites	[332,333]
Inhibitor	RU.521, PF-06928215, Compound C20, G140	Occupies the cGAS catalytic site	[334,354,355]
Inhibitor	CU-32, CU-76	Inhibits cGAS enzymatic activity	[356]
Antagonist	VENT-03	Inhibits the enzymatic activity of cGAS	[347]

cGAS: Cyclic GMP-AMP synthase; dsDNA: Double-stranded DNA.

Table 2: Agonists and inhibitors of STING.

Type	Name	Mechanism	References
CDN agonist	c-di-AMP, c-di-GMP, 2',3'-cGAMP, 3',3'-cGAMP, IACS-8803, IACS-8779, MK-1454	Induces STING conformational change	[338,340,357–360]
CDN agonist	BI 7446	Activates five STING variants	[339]
Non-CDN agonist	diABZI, MSA-2, DMXAA, SR-717, E7766, G10	Induces STING conformational change	[117,200,343,344,361,362]
Non-CDN agonist	CF502	Increases STING phosphorylation	[363]
Inhibitor	SN-011	Occupies the CDN-binding pocket	[364]
Inhibitor	STING-IN-7	Inhibits STING phosphorylation	[365]
Inhibitor	C-170, STING-IN-3, STING-IN-11, C-176, C-178	Inhibits STING palmitoylation	[337,346,366,367]

cGAMP: Cyclic GMP-AMP; CDN: Cyclic dinucleotide; STING: Stimulator of interferon genes.

Table 3: Clinical trials targeting the cGAS–STING signaling pathway.

Name	Target	Tagert diseases	Patient population	Primary endpoints	Results	Phase (Trial ID)
VENT-03	cGAS	SLE, SS ^[347]	–	–	–	–
RBS2418	cGAMP	CRC	150	Progression-free survival (PFS)	–	II (NCT06824064)
CRD3874-SI	STING	Malignant solid tumors	72	Maximum tolerated dose	–	I (NCT06021626)
IMSA101	STING	Metastatic kidney cancer	15	PFS rate associated with the therapeutic intervention	–	I (NCT06601296)
SYNB1891	STING	Advanced malignan-cies ^[348]	32	Number of participants with dose-limiting toxicity	Safe and well tolerated	I (NCT04167137)
MIW815	STING	Advanced solid tum-ors, lymphomas ^[353]	106	Incidence of dose-limiting toxicities	Minimal efficacy with refractory cancers	I (NCT03172936)
E7766	STING	Nonmuscle invasive bladder cancer	–	Number of participants with dose-limiting toxicities	–	I (NCT04109092)
		Advanced solid tum-ors, lymphomas ^[349]	24		On-target activity	I (NCT04144140)
Baricitinib	STING	SAVI ^[351]	10	Change from baseline in mean daily diary scores	A positive benefit/ risk profile	II/III (NCT04517253)
		Autoinflammatory syndromes ^[350]	–	–	Clinical and inflam-matory improved	III (NCT01724580)
CRD3874	STING	Acute myeloid leukemia	32	Safety and tolerability by multiplex cytokine profiling	–	I (NCT06626633)
SNX281	STING	Advanced solid tum-ors and lymphoma	27	Incidence of dose-limit-ing toxicities	–	I (NCT04609579)
TAK-500	STING	Advanced or meta-static solid tumors	61	Overall response rate	–	I (NCT05070247)
STAV	STING	Aggressive leukemias	–	Percentage of partici-pants achieving clinical complete response	–	I (NCT05321940)
GSK3745417	STING	Advanced solid tumors	97	Number of participants achieving dose-limiting toxicity	–	I (NCT03843359)
ONM-501	STING	Advanced solid tumors, lymphomas	168	Number of participants reporting one or more treatment-emergent adverse events	–	I (NCT06022029)

cGAMP: Cyclic GMP-AMP; CRC: Colorectal cancer; SLE: Systemic lupus erythematosus; STING: Stimulator of interferon genes; –: The clinical results remain undisclosed.

on Mn²⁺-mediated activation of the cGAS–STING signaling pathway.^[321–324] These findings demonstrate the tremendous therapeutic potential of Mn²⁺.

The utilization of Zn²⁺ has also yielded encouraging results. Zn²⁺ significantly upregulates cGAS/STING expression,^[325] synergizing with ferroptosis to increase immunogenic cell death and remodel the immunosuppressive TME.^[326] Zn²⁺ activates the cGAS–STING signaling pathway to achieve dual suppression of oxidative phosphorylation and glycolytic metabolism in breast cancer, thereby inducing tumor cell death^[327] [Table 1].

β-Arrestin 2 modulates diverse cellular processes through G protein-coupled receptor signaling pathways. Specifically, β-arrestin 2 interacts with cGAS to increase dsDNA binding, thereby increasing cGAMP production and ultimately facilitating viral clearance^[328] [Table 1].

Chitosan represents an attractive alternative to alum in vaccine adjuvants because of its composition of N-acetylated and deacetylated glucosamine units. This biopolymer can trigger intracellular DNA release, thereby activating cGAS and initiating the cGAS–STING signaling pathway.^[329,330] [Table 1]. Manganese-coordinated chitosan (CS-Mn) microparticles with selective DNA-capturing capability enable efficient DNA delivery in the presence of serum while synergizing with Mn²⁺ to activate the cGAS–STING signaling pathway in DCs.^[331]

Inhibitors of cGAS

A growing number of novel cGAS inhibitors have been reported, with mechanisms of action that can be categorized into two classes [Table 1]: (1) blocking DNA-binding sites on cGAS and (2) inhibiting the catalytic site of cGAS and suppressing its enzymatic activity. Disrupting

the binding between cGAS and dsDNA represents one strategy to inhibit cGAS activation. Suramin can displace DNA bound to cGAS,^[332,333] thereby suppressing cGAS activation and downstream signaling molecule production. Another inhibitor suppresses cGAMP production by targeting both the catalytic site and the enzymatic activity of cGAS. For example, RU.521 alleviates acute inflammation and mitigates chronic inflammation with associated tracheal fibrosis in patients with benign airway stenosis by suppressing cGAS activity.^[334]

Agonists and inhibitors of STING

Agonists of STING

Given the immunostimulatory potential of the cGAS–STING signaling pathway, the development and therapeutic application of STING agonists are critically important in cancer treatment. STING agonists can be classified into CDN-based agonists and non-CDN-based agonists^[335] [Table 2]. Despite structural differences, both classes activate STING by inducing conformational changes that drive its oligomerization and downstream signaling.

Natural CDNs, including c-di-AMP, c-di-GMP, 3',3'-cGAMP, and 2',3'-cGAMP, serve as endogenous STING agonists and are widely utilized in antitumor and antiviral research. The Bacille Calmette–Guérin vaccine strain overexpressing c-di-AMP has enhanced immunogenicity and superior efficacy against bladder cancer.^[336] C-di-GMP elicits a potent STING-dependent antiviral transcriptional response in *Drosophila melanogaster*.^[249] Tumor-derived exosomal ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1) hydrolyzes 2',3'-cGAMP to suppress cGAS–STING signaling.^[337] Natural CDNs have several limitations, including susceptibility to enzymatic degradation, poor membrane permeability, and significant side effects. Synthetic CDN analogs have been developed to address these challenges. Two 2',3'-phosphorothioate-CDA analogs, IACS-8779 and IACS-8803, demonstrate potent STING signaling pathway activation and elicit robust systemic antitumor responses *in vitro*.^[338] Low-dose intratumoral injection of BI 7446 in mice induces durable, tumor-specific immune-mediated rejection.^[339] MK-1454 exhibited robust tumor cytokine upregulation and effective antitumor activity.^[340]

A growing number of non-CDN STING agonists have been reported, demonstrating promising therapeutic potential. diABZI-mediated STING activation enhances immunotherapy efficacy in AML.^[341] ABZI represents the first potent non-CDN STING agonist demonstrating systemic antitumor activity in murine models and is regarded as the most promising non-CDN STING activator to date.^[342] Other non-CDN STING agonists, including MSA-2,^[200] DMXAA,^[343] and E7766,^[344] have also demonstrated promising antitumor efficacy.

Inhibitors of STING

To date, two primary approaches have been used to identify STING inhibitors [Table 2]. The first strategy involves

designing molecules that occupy the CDN-binding pocket, thereby acting as competitive antagonists of STING activators. The second approach focuses on identifying inhibitors that bind to residues near the transmembrane domain of STING, consequently interfering with its conformational changes. We systematically evaluated both classes of inhibitors, beginning with a concise overview of inhibitor design principles followed by a detailed characterization of representative STING inhibitors.

Compared with the endogenous cGAS product 2',3'-cGAMP, SN-011 has a superior binding affinity to the CDN-binding pocket, locking STING dimers in an open, inactive conformation.^[345] In multiple *in vitro* models of STING activation, including 2',3'-cGAMP stimulation, HSV-1 infection, *Trex1* deficiency, and cGAS–STING protein overexpression, SN-011 consistently suppresses interferon and inflammatory cytokine induction in both mouse and human cellular systems.^[345]

The compounds C-176 and C-178 selectively target transmembrane cysteine residue 91, effectively blocking activation-induced STING palmitoylation.^[346] This inhibition prevents the oligomerization of STING into multimeric complexes at the Golgi apparatus, ultimately suppressing the STING-mediated production of inflammatory cytokines in both human and murine cells.

Clinical trials targeting the cGAS–STING signaling pathway

Targeting the cGAS–STING signaling pathway holds promising therapeutic potential, particularly with STING agonists [Table 3]. The cGAS inhibitor VENT-03 is scheduled to initiate phase I clinical trials for SLE and systemic sclerosis.^[347] A CRC clinical trial of RBS2418 (NCT06824064), an inhibitor of cGAMP hydrolysis, is currently underway. Repeated intratumoral injections of SYN1891 (NCT04167137), both as monotherapy and in combination with atezolizumab, were found to be safe and well tolerated, with evidence of STING signaling pathway target engagement.^[348] E7766 (NCT04144140) has demonstrated target-specific pharmacodynamic effects in patients with solid tumors.^[349] Baricitinib (NCT04517253, NCT01724580) may represent a potential therapeutic option for patients with STING-associated vasculopathy with onset in infancy (SAVI), demonstrating a favorable benefit-risk profile in this vulnerable population with multiple comorbidities.^[350,351] Although MIW815 achieved durable tumor regression in multiple murine tumor models, the results of a clinical trial (NCT03172936) were disappointing.^[352,353] Phase I clinical trials of SNX281 and TAK-500 for solid tumors and lymphomas have recently been completed (NCT04609579, NCT05070247), although the clinical results remain undisclosed. Additional agonists, including CRD3874-SI, CRD3874, GSK3745417, STAV-1, IMSA101, and ONM-501, are currently under clinical evaluation (NCT06021626, NCT06626633, NCT03843359, NCT05321940, NCT06601296, and NCT06022029).

The clinical translation of the cGAS–STING pathway faces multifaceted, interdisciplinary challenges. Drug delivery and targeting constitute a critical bottleneck:

systemic administration often triggers non-specific inflammation (e.g., cytokine release syndrome), penetration into solid tumors is difficult, and endogenous cGAMP is readily degraded by the extracellular enzyme ENPP1. The inherent biological complexity further impedes progress: the pathway exhibits a dual nature—moderate activation exerts anti-tumor effects, while excessive activation promotes immunosuppression; pronounced human-mouse species differences (e.g., in ligand sensitivity: hSTING/cGAMP *vs.* mSTING/DMXAA) significantly diminish the predictive value of preclinical data. Clinical development hurdles are prominent: a narrow therapeutic window (where effective doses approach toxic levels), the absence of reliable biomarkers, and the complexity of combination therapy regimens. From a medicinal chemistry perspective, small-molecule agonists suffer from poor stability and membrane permeability barriers, while inhibitor development remains in its early stages. Pathways forward hinge on the following: (1) Innovative strategies: developing targeted delivery systems, allosteric modulators, and optimized combination therapies. (2) Emerging technologies: leveraging multi-omics approaches (e.g., single-cell genomics, spatial transcriptomics) to identify robust biomarkers at the level of cellular subsets and spatial distribution. (3) AI-driven acceleration: expediting target discovery, virtual screening, and generative molecular design/optimization; accurately predicting pharmacokinetics/toxicity to de-risk compounds early; optimizing clinical trial patient stratification and drug repurposing strategies, thereby significantly enhancing efficiency and success rates.

Perspectives and Conclusions

The cGAS–STING signaling pathway has achieved significant breakthroughs in understanding its functions, signal transduction mechanisms, and regulatory networks. As a crucial component of the innate immune system, the cGAS–STING signaling pathway detects cytosolic DNA. Subsequently, it triggers inflammatory gene expression, thereby inducing cellular senescence or activating defense mechanisms. The remarkable ability of cGAS–STING lies in its ability to recognize both exogenous DNA (from viruses, bacteria, and parasites) and endogenous DNA (aberrant nuclear DNA and mtDNA), leading to STING activation and downstream signaling cascades. Research has revealed that this pathway is involved in the pathogenesis of various diseases, including infections, cancers, autoimmune disorders, and systemic diseases. The cGAS–STING signaling pathway is regulated through multiple posttranslational modifications, such as phosphorylation, ubiquitination, and palmitoylation. These advances have led to the development of multiple pharmacological modulators (both agonists and inhibitors) of the cGAS–STING signaling pathway, which have shown significant efficacy in preclinical and clinical studies. Collective evidence has established the cGAS–STING signaling pathway as a central regulatory node in disease pathogenesis and treatment strategies.

However, the roles of the cGAS–STING signaling pathway in many disease contexts remain unclear and warrant further investigation. First, as the cGAS–STING signaling pathway plays critical roles across multiple cell types, organs, and physiological systems, achieving targeted

therapy while minimizing off-target effects on healthy tissues remains a major challenge. Current agonists and inhibitors lack precise targeting, often disrupting homeostasis in nondiseased cells/organs/systems during treatment. Using single-cell technologies and spatial omics to delineate the expression profiles and mechanisms of cGAS–STING across different cell types, organs, and systems will be crucial. This approach, combined with the development of novel targeted drug delivery methods, should establish the foundation for the development of specific therapeutic interventions. In addition, current clinical trials have focused primarily on cancer and tumors, while compelling evidence for its clinical efficacy in other systemic diseases, particularly inflammatory disorders, is still lacking. Although existing data demonstrate the promising therapeutic potential of various drugs in mouse models and *in vitro* systems, their clinical performance has been disappointing. Future studies should expand clinical trial cohorts to validate the therapeutic effects of cGAS–STING agonists and inhibitors rigorously. Third, while current evidence suggests that cytosolic DNA activates the cGAS–STING signaling pathway, several fundamental questions remain unresolved: can all cytosolic DNA species activate cGAS, and does the precise subcellular localization of cGAS activation occur? Therefore, future studies should systematically characterize the types and molecular features of cytosolic DNA capable of triggering cGAS activation. Elucidating these mechanisms may reveal novel therapeutic strategies and molecular targets for clinical intervention. Concurrently, the clinical translation of the cGAS–STING signaling pathway has accelerated through the development of innovative strategies—including targeted delivery systems, allosteric modulators, and optimized combination therapies—the application of emerging technologies such as single-cell multi-omics and spatial transcriptomics, and the integration of AI-driven drug discovery and development.

In conclusion, the cGAS–STING signaling pathway orchestrates the activation of multiple interconnected processes, including inflammation, cell death, and immune responses, and engages numerous downstream molecules and cross-regulatory pathways. Both excessive activation and suppression of the cGAS–STING signaling pathway can disrupt normal immune homeostasis. In contexts such as tumors and viral infections, impaired cGAS–STING signaling typically contributes to disease progression. Conversely, in various systemic disorders, hyperactivation exacerbates inflammatory signaling and promotes pathogenic cell death. These dichotomous effects highlight the therapeutic potential of precisely modulating STING activity. Developing targeted agonists and inhibitors capable of maintaining STING homeostasis *in vivo* represents a promising new avenue for clinical intervention. Such precision therapeutics could establish balanced signaling pathway regulation that is sufficiently robust to combat disease yet restrained enough to prevent collateral tissue damage.

Acknowledgments

We thank Chong Zhao, Wenting Dai, and Fangfang Wang for their guidance in drawing and performing the literature search.

Funding

This work was supported by grants from the National Natural Science Fund of China (Nos. 82322011, 82170623, 82170625, 82300711, and 82470648), and the “135” projects for disciplines of excellence of West China Hospital, Sichuan University (Nos. ZYYC23026 and ZYGD23029).

Conflicts of interest

None.

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How to cite this article: Xiao Y, Ma YF, Zhao JH, Zhang XY, Gan C, Gao JH, Huang ZY. cGAS–STING signaling pathway as a therapeutic target in human diseases. *Chin Med J* 2025;138:3251–3284. doi: 10.1097/CM9.0000000000003904