cGAS/STING pathway and gastrointestinal cancer: Mechanisms and diagnostic and therapeutic targets (Review)

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Abstract. The health of individuals is seriously threatened by intestinal cancer, which includes pancreatic, colorectal, esophageal, gastric and gallbladder cancer. Most gastrointestinal cancers do not have typical and specific early symptoms, and lack specific and effective diagnostic markers and treatment methods. It is critical to understand the etiology of gastrointestinal cancer and develop more efficient methods of diagnosis and treatment. The cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) pathway serves a crucial role in the occurrence, progression and treatment of gastrointestinal cancer. The present review focuses on the latest progress regarding the role and mechanism of the cGAS/STING pathway in gastrointestinal cancer, and discusses treatment approaches and related applications based on the cGAS/STING signaling pathway. In order to improve the knowledge of the connection between the cGAS/STING pathway and gastrointestinal cancer, aid the diagnosis and treatment of gastrointestinal cancer, and lessen the burden on patients and society, the present review also discusses future research directions and existing challenges regarding cGAS/STING in the study of gastrointestinal cancer.

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Contents

1. Introduction

Gastrointestinal cancer accounts for one-quarter of the global incidence rate of cancer and one-third of cancer-related deaths (1). The efficacy of various treatment approaches is restricted due to unidentified mechanisms, adverse effects and cancer resistance. Therefore, it is crucial to elucidate the pathogenesis and develop novel therapeutic targets (2).

The cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) pathway has become a key regulatory pathway for cancer (3,4). Once cGAS/STING binds to DNA, it can stimulate various immune defense mechanisms and virtually influence every facet of the development of cancer, such as the malignant cell transformation, occurrence, development, drug resistance, metastasis and recurrence (3,5). Previous studies have reported that activation of the cGAS/STING pathway is related to the maintenance of gastrointestinal homeostasis (6,7). An increasing number of studies have found that the cGAS/STING pathway serves an important regulatory role in gastrointestinal cancer (7-11). However, the exact role and molecular mechanisms of the cGAS/STING pathway in gastrointestinal cancer, as well as its mechanistic clinical applications, still need to be elucidated.

The present review discusses the critical role that the cGAS/STING signal serves in the processes pertaining to the occurrence, progression, diagnosis and treatment of gastrointestinal cancer, as well as how cGAS/STING leads to beneficial or harmful outcomes of gastrointestinal cancer. The present review considers the current follow-up research directions and challenges regarding the cGAS/STING axis in gastrointestinal cancer, and emphasizes the novel frontiers of cGAS/STING biology to inspire individuals to consider their association with gastrointestinal cancer.

2. cGAS/STING pathway and gastrointestinal cancer

Gastrointestinal cancer includes gastric, colorectal, esophageal, liver, gallbladder and pancreatic cancer. Although the cGAS/STING pathway serves a crucial role in maintaining gastrointestinal homeostasis, overactivation of the cGAS/STING pathway can lead to gastrointestinal cancer and other gastrointestinal diseases (7-11). The development of novel treatment approaches for gastrointestinal malignancies may benefit from elucidating the molecular mechanisms and effects of the cGAS/STING pathway in gastrointestinal cancer (7).

Increasing evidence suggests that the cGAS/STING pathway serves a crucial role in the initiation, progression and treatment of gastrointestinal cancer (7-11). Fig. 1 briefly summarizes the scope of the influence of this important pathway, and aims to visually represent which cancer types are affected by the cGAS/STING pathway, and the specific physiological and pathological processes that are impacted. Numerous studies have shown that the cGAS/STING pathway serves an important role in various gastrointestinal cancer types, including gastric, colorectal, pancreatic, liver and esophageal cancer (8-10). The occurrence, progression, diagnosis, therapy, prognosis and immune regulation of these cancer types are all influenced by the cGAS/STING pathway (8-10). Further exploration of the role of the cGAS/STING pathway in these cancer types may provide novel strategies for the diagnosis and treatment of digestive tract cancers.

Effects of the cGAS/STING pathway in gastric cancer. Gastric cancer is one of the most prevalent malignant tumors of the digestive tract that primarily originates from the gastric mucosa and is a danger to the health of individuals. According to statistics for 2021, there were ~1.089 million new cases and 768,000 deaths worldwide each year (12). Due to the lack of obvious and specific stage symptoms in the early stage of gastric cancer, the majority of patients with gastric cancer are diagnosed in the advanced stage and their prognosis is frequently poor (13,14). It is imperative to investigate novel diagnostic and therapeutic approaches and to clarify the processes underlying the onset and progression of stomach cancer.

Shen *et al* (15) indicated that metformin has potential in cancer immunotherapy by inhibiting the SOX2/AKT axis, which activates the cGAS/STING pathway. Research has found that activating cGAS/STING signaling and targeting MUS81 structure specific endonuclease subunits can enhance the anticancer effect of WEE1 in gastric cancer (16). These data suggested that targeting cGAS/STING may be a promising clinical strategy for the treatment of gastric cancer. Yuan *et al* (17) reported the mechanism of anlotinib in gastric cancer treatment via the cGAS/STING pathway. Their experimental results demonstrated that anlotinib inhibited gastric cancer cell proliferation, migration and immune escape by activating the cGAS/STING/IFN-β pathway. Yang *et al* (18) created a prediction model based on genes linked to the cGAS/STING pathway to forecast the prognosis of gastric cancer, offering a novel viewpoint for the assessment of recurrence risk and prognosis. It has been reported that HER2 signaling may inhibit immune cell activation in the cancer microenvironment of gastric cancer by inhibiting STING signaling in cancer cells in HER2-positive gastric cancer (19). The cGAS/STING pathway, which is responsible for producing IFN-β and activating anticancer immunity, is activated by anti-CD47 therapy (20). These findings provide a promising novel strategy for CD47-targeted immunotherapy in gastric cancer associated with Epstein-Barr virus. Hosseinzadeh *et al* (21) suggested that a combination therapy using IFN-γ, STING agonist and anti-programmed cell death protein 1 (PD-1) antibody provided a promising method for the treatment of gastric cancer. The cGAS/STING signaling-mediated senescence-associated secretory phenotype pathway has recently been identified in the promotion of gastric cancer, and p53 and replication protein A2 are highly expressed in gastric cancer (22).

Although the cGAS/STING pathway exists and serves a crucial role in various cell types, there may be differences in the activation and response to this pathway among different cell types (8,17). These differences may stem from various factors such as genetic background, physiological state and microenvironment among cells. In some cases, different cells may require different ligands or stimulatory signals to activate the cGAS/STING pathway and achieve the same effect (16,17). This may be related to the distribution of receptors on the cell surface, differences in signal transduction pathways and the expression of downstream effector molecules. Even under the action of the same ligand, different cells may produce different biological effects through different signal transduction pathways (9,17). This may be related to the complexity of the intracellular signaling network and the interactions between signaling molecules. For instance, during the activation of the cGAS/STING pathway with additional dynamin-related protein 1 (Drp1), some esophageal squamous cell carcinoma cell types may shift to a proliferative state (8). Conversely, HS746T cells inhibited by anlotinib, after returning from a proliferative state to a reference state, also undergo transitions during cGAS/STING activation (17). These changes may be related to multiple factors such as intracellular signal transduction pathways, gene expression regulation and cellular metabolic state (8,17).

Future research needs to further explore the specific mechanisms of the cGAS/STING pathway in different cell types and how to utilize this pathway in disease treatment and immunotherapy applications.

Gastric cancer lacks effective early diagnostic markers and treatment methods. Research has revealed that the cGAS/STING signal serves a crucial role in the initiation, progression and treatment of gastric cancer. The cGAS/STING pathway can influence the state of immune cells, the activation of immune pathways, DNA damage repair, the proliferation and migration of gastric cancer cells, and other processes during the initiation and progression of gastric cancer by regulating the transduction of various molecules and signaling pathways such as SOX2/Akt, C-X-C motif chemokine ligand (CXCL)9/10/11 and IFN-β (Fig. 2). Effective diagnostic and therapeutic methods based on the aforementioned roles of the cGAS/STING pathway require targeted and in-depth research. Such research can provide novel insights for the early diagnosis and effective treatment of gastric cancer, thereby alleviating the burden on patients with gastric cancer and improving their quality of life.

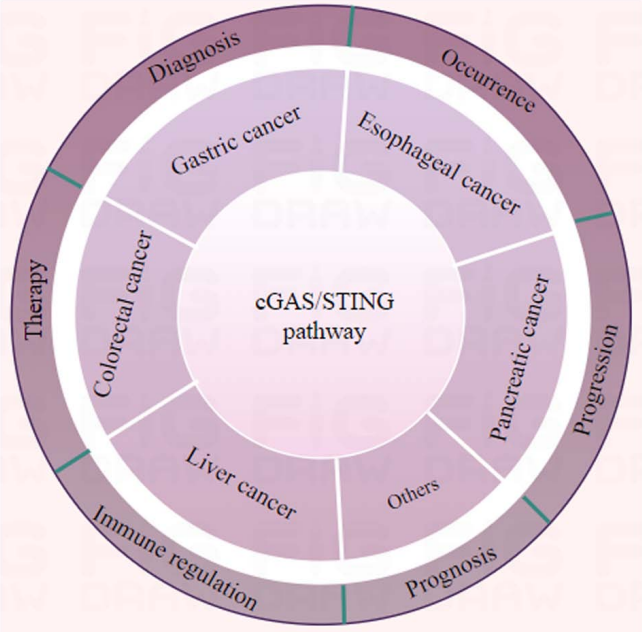

Figure 1. cGAS/STING pathway and gastrointestinal cancers. The figure was generated using Figdraw2.0 (https://www.figdraw.com/static/index.html#/paint_index_v2). cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes.

cGAS/STING signaling regulates the initiation and progression of esophageal cancer. Esophageal cancer is the eighth most common malignant tumors and one of the leading causes of cancer-related deaths worldwide (7). The 5-year relative survival rate for patients with esophageal cancer is still <20% despite progress in various treatment methods, including surgical resection, immunotherapy, radiotherapy and chemotherapy (7,23). Improved treatment strategies and patient prognosis may be achieved by understanding the pathogenesis of esophageal cancer.

Li *et al* (8) revealed that upregulation of Drp1 induced mitochondrial dysfunction and cytoplasmic mitochondrial DNA (mtDNA) stress, followed by activation of the cGAS/STING pathway, triggering autophagy and promoting esophageal squamous cell carcinoma progression. This investigation provided novel insights into the molecular mechanisms of mitochondrial dynamics and the progression of esophageal squamous cell carcinoma. It has been reported that mitochondrial disruption-induced mtDNA stress regulates cGAS/STING pathway activity and autophagy to promote esophageal squamous cell carcinoma growth, revealing an underutilized therapeutic strategy for esophageal squamous cell carcinoma (24). The intrinsic expression of cGAS/STING in cancer cells serves an important regulatory role in radiation-induced immune cell activation in the tumor microenvironment, and also participates in the recruitment process of cancer-promoting M2-tumor-associated macrophages (M2-TAMs) in esophageal cancer (25). Targeting IL-34 to block M2-TAM infiltration may improve the therapeutic effects of radiation therapy and the efficacy of radiation therapy combined with immune checkpoint inhibitors in the treatment of esophageal cancer (25). Matsuishi *et al* (26) revealed that chemotherapy drugs, specifically 5-fluorouracil and cisplatin, activated the cGAS/STING pathway in esophageal squamous cell carcinoma cells. This activation led to the expression of type I interferon and T cell-related chemokines, suggesting that the inherent cGAS/STING pathway within cancer cells may serve a role in chemotherapy-induced immune cell activation in esophageal squamous cell carcinoma (26). It has been reported that the intrinsic cyclic cGAS/STING pathway in esophageal cancer cells is implicated in the activation of the antitumor immune response induced by radiotherapy (27). However, to the best of our knowledge, its contribution to alterations in tumor microenvironment remodeling induced by radiotherapy in esophageal cancer remains largely unexplored. Nakajima *et al* (27) found that the inherent cGAS/STING pathway in esophageal cancer cells was a key component of radiotherapy-induced immune cell activation in the tumor microenvironment by inducing type I interferon and CXCL10 in esophageal cancer. DNA polymerase θ (POLQ) deficiency inhibits the growth of esophageal cancer and promotes genomic instability via the cGAS/STING/interferon-stimulated gene pathway (28). The STING-interferon α and β receptor subunit 1/STAT1/interferon regulatory factor 1 axis regulates immune responses triggered by fractionated irradiation in esophageal cancer cells, and the STING pathway also contributes to immune cell invasion of esophageal cancer cells (29). Radiation therapy is a widely used treatment strategy for esophageal squamous cell carcinoma; however, the radiation resistance of tumor tissues and its side effects on normal tissues have limited its development. A novel lipid-modified manganese diselenide nanoparticle has been developed, which increases radiosensitivity through cGAS/STING-mediated immune stimulation and chemodynamic therapy, and protects normal tissues against radiation to optimize esophageal cancer therapy (30).

Increasing evidence has demonstrated the regulatory effect of the cGAS/STING pathway in esophageal cancer (27-30). The mechanisms that dictate the function of the cGAS/STING pathway vary in different contexts; for example, cGAS/STING can affect the efficacy of radiotherapy, proliferation or immune regulation in different situations (27-29). A deeper understanding of the roles and mechanisms of the cGAS/STING pathway in different contexts will aid the development of cGAS/STING signaling modulatory therapies. Inhibiting the cGAS/STING pathway may be beneficial for the treatment of esophageal cancer (28,29). Future studies are required to enable medical professionals to select the appropriate cGAS/STING modulators based on the particular circumstances.

Role and mechanism of cGAS/STING in colorectal cancer. Colorectal cancer is a commonly diagnosed type of cancer, with an estimated 592,232 new cases in 2022 worldwide, and was the fifth most common cause of cancer deaths in China in 2022 (31,32). Despite the rapid development of treatment methods for colorectal cancer, including immunotherapy, chemotherapy and radiation therapy, there is still no cure. The effectiveness of existing treatment methods is not satisfactory as the median overall survival time of patients with colorectal cancer is ~30 months (32). Understanding the numerous processes involved in the initiation and progression of colorectal cancer at the cellular and molecular levels is crucial for developing precise and efficient therapeutic strategies.

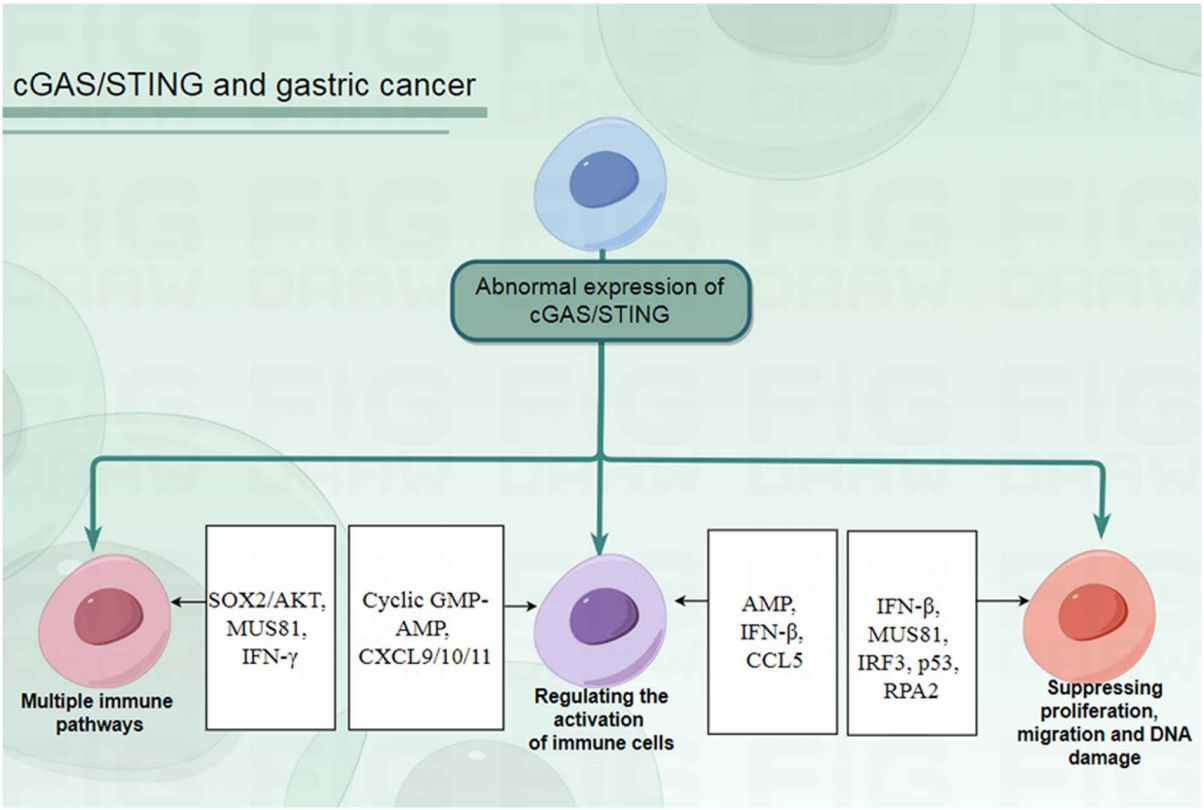

Figure 2. cGAS/STING signaling regulates the initiation and progression of gastric cancer. The figure was generated using Figdraw2.0. CCL5, C-C motif chemokine ligand 5; cGAS, cyclic GMP-AMP synthase; CXCL, C-X-C motif chemokine ligand; IRF3, interferon regulatory factor 3; MUS81, MUS81 structure-specific endonuclease subunit; RPA2, replication protein A2; STING, stimulator of interferon genes.

In some cases, local radiation therapy may produce T cell-mediated abscopal effects on non-irradiated cancer lesions, especially when combined with immune checkpoint blockade (33). However, this effect is still rare in clinical practice, and improvements and further clarification are highly desirable. The abscopal effect is dependent on cancer cell mitochondrial DNA and cGAS/STING, which is enhanced by the addition of liposome doxorubicin (33). Wang *et al* (9) determined that the germline polymorphism of STING and IFNB1 genes may predict the efficacy of cetuximab treatment in patients with metastatic colorectal cancer. The cGAS/STING pathway axis in colon adenocarcinoma could regulate the m6A and m5C modifications of glutathione peroxidase 4, which could be a promising target for immunotherapy in colorectal cancer (34). Protecting the nuclear membrane and genomic integrity of colorectal cancer cells delayed the progression of colorectal cancer by preventing the activation of the cGAS/STING axis via heterochromatin protein 1γ (35). Hu *et al* (36) found that the absence of cGAS in mice exacerbated chemically induced colon cancer associated with colitis. Mice lacking cGAS were more susceptible to colitis-associated colon cancer infection than mice lacking STING or type I interferon receptors under the same conditions (36). SH2 domain-containing tyrosine phosphatase 2 (SHP2) regulates the dephosphorylation of poly(ADP-ribose) polymerase 1 (PARP1) in colon cancer, thereby inhibiting DNA repair and enhancing the anticancer immunity mediated by the cGAS/STING pathway (37). This suggests that SHP2 may serve as a promising therapeutic target for colon cancer treatment. It has been reported that barrier to autointegration nuclear assembly factor 1-knockout activated an anticancer immune response effect regulated by the cGAS/STING pathway, resulting in immune activation within the tumor microenvironment (38). This activation manifested as increased infiltration of $CD8^+$ T cells and decreased accumulation of bone marrow-derived suppressive cells (38). The detection of the expression levels of cGAS and STING indicated that the staging and metastasis of colorectal cancer are closely related to the activation status of the cGAS/STING signaling pathway (39). In multiple colorectal cancer models, Vornholz *et al* (40) found that the superior antitumor immune response in mismatch repair-deficient colorectal cancer required activation of the cGAS/STING signal in colorectal cancer cells. The research findings introduced a reasonable strategy to forcibly regulate the intrinsic program of cancer cells by engineering STING, making drug-resistant tumors sensitive to immune checkpoint inhibitors (40).

Drug activation of cGAS/STING in the tumor environment is considered an attractive and promising tumor therapy for colorectal cancer; however, its efficacy is limited in clinical practice (41). STING expression in colorectal cancer cells was enhanced by lysine demethylase 5 inhibitors and inhibited cancer growth in immunocompromised mice (41). HER2 is a protein that is frequently upregulated in various cancer types, including colorectal cancer (32). The HER2-targeted antibody monomethyl auristatin E conjugate RC48 made HER2-positive colon cancer cells more susceptible to immunotherapy by activating the cGAS/STING signaling (32). A study involving 1,424 patients with colorectal cancer revealed

that the toll like receptor 3/cGAS/STING/IKKε/TANK binding kinase 1/IFN signal axis serves an important role in the occurrence and development of colorectal cancer (42). In the absence of colon cancer cell-induced STING, higher doses of 5-fluorouracil are needed to alleviate the tumor burden (43). In human colorectal specimens, higher STING expression was associated with higher survival rates (43). Liang *et al* (44) indicated that SIX homeobox 4 was the main regulatory factor for STING expression in colon cancer cells. This observation offers supplementary mechanisms and genetic markers that can aid in predicting effective responses to immune checkpoint blockade therapy. The combination of lovastatin and cGAS/STING axis stimulation mediated by liposome delivery systems enhanced colorectal cancer immunotherapy and chemotherapy, providing a novel clinical diagnosis and treatment strategy for combined immune checkpoint blockade treatment of 'immune cold' cancers (45). The immune checkpoint inhibitor response in colorectal cancer is enhanced by dietary methionine restriction, and the cGAS/STING pathway serves a crucial regulatory role in this process (46). The cGAS/STING pathway could also be triggered in combination with photothermal ablation therapy to achieve improved therapeutic outcomes in colorectal cancer (47).

Numerous studies have been conducted on the molecular and cellular mechanisms of the relationship between cGAS/STING and colorectal cancer (32,43-47) (Table I), as well as the effects of radiotherapy and chemotherapy, prognosis prediction, clinical association analysis, and drug development. However, clinical application of cGAS/STING in the diagnosis and treatment of colorectal cancer is still limited, and researchers need to strengthen related clinical research and drug development in later research to benefit more patients with colorectal cancer.

Role of the cGAS/STING pathway in liver cancer. Liver cancer is one of the most common malignant tumors of the digestive system worldwide and a major cause of cancer-related deaths (48). Although scientists and medical professionals have performed numerous studies investigating the diagnosis, management and treatment of liver cancer, the prognosis is still poor and the mortality rate is high, and thus, it is necessary to explore the pathogenesis and novel treatment strategies (48,49). The cGAS/STING pathway has a significant effect in liver physiology and pathology, and is closely related to the occurrence, progression and treatment of liver cancer (48,50). The present review provides a summary highlighting the significance of the cGAS/STING pathway in the occurrence and progression of liver cancer, as well as the efficacy of targeting cGAS/STING in liver cancer treatment and its synergistic potential with other therapeutic modalities in clinical practice (Table II). The aim is to offer novel insights for the diagnosis and management of liver cancer.

Hyperbaric oxygen promotes cGAS/STING activation induced by teniposide to enhance the anticancer effect of PD-1 antibody in hepatocellular carcinoma (51). Enhancing DNA-activated STING signaling by reducing hypoxia may be a possible direction to improve the incidence of adverse reactions to PD-1 antibody in patients with hepatocellular carcinoma. Using a combination of multiple therapies for the treatment of advanced hepatocellular carcinoma has become a major trend. Wang *et al* (52) reported that sorafenib combined with STAT3 knockdown triggered endoplasmic reticulum stress-induced apoptosis of hepatocellular carcinoma cells and that the cGAS/STING pathway elicited antitumor immunity. Persistent DNA damage caused by deficiencies in the BRCA pathway induces tumor immune suppression and T lymphocyte infiltration in hepatocellular carcinoma via the cGAS/STING pathway (53). This insight provides a more profound understanding of the remodeling of the tumor immune microenvironment, such as sustained DNA damage inducing tumor immunosuppression and T lymphocyte infiltration, which could potentially enhance the response of hepatocellular carcinoma to PD-1 therapy. Intelligently responsive Fe/Mn nanovaccines could be used for liver cancer immunotherapy and induced immunogenic cell death by triggering pyroptosis-boosted cGAS/STING pathway activity in cellular and mouse models (54). The gut microbiota could regulate radiation-related anti-liver cancer immune responses via the cGAS/STING pathway, which could serve a key role in the treatment of liver cancer (55). RADA16-I (R) peptide was dissolved in a mixture of lyOK-432 (O) and doxorubicin (D) to develop an ROD hydrogel. The novel ROD peptide hydrogel could induce anticancer immunity by activating the cGAS/STING/IFN-I pathway, which can effectively treat residual liver cancer after incomplete radiofrequency ablation of liver cancer (56). The cGAS/STING signaling pathway serves an important regulatory role in the anticancer effect of AZD6738, which enhances the tumor immune microenvironment of hepatocellular carcinoma to enhance the antitumor activity of radiotherapy and immune checkpoint inhibitors (57). A study has found that RecQ like helicase 4 derived from hepatocellular carcinoma cells inhibited the cGAS/STING pathway in dendritic cells by regulating the DNA repair process, reducing the sensitivity of hepatocellular carcinoma to radiation (58).

The regulation of the STING pathway has been found to affect the development of hepatocellular carcinoma by regulating STAT1/programmed death-ligand 1 (PD-L1)/IFN in *in vitro* and *in vivo* models (59). The regulation of the STING pathway serves a crucial role in the development of hepatocellular carcinoma and has been expected to be used as a treatment for hepatocellular carcinoma, most likely in combination with other immunomodulatory therapies or standard care (59). By targeting eukaryotic elongation factor 2 kinase blockade, it may be possible to activate the cGAS/STING pathway, thereby enhancing the activity of natural killer (NK) cells in hepatocellular carcinoma (60). This presents a novel strategy for the treatment of this disease. Recombinant oncolytic influenza virus expressing PD-L1 antibody induced activation of $CD8^+$ T cells in hepatocellular carcinoma mice via the cGAS/STING pathway, thereby killing cancer cells (61). Isopentenyl-diphosphate δ isomerase 1 interacts with cGAS and recruits the E3 ligase tripartite motif containing 41 to promote ubiquitination and degradation of cGAS, thereby inhibiting the cGAS/STING signaling pathway (62). This process serves a crucial regulatory role in the progression of hepatocellular carcinoma. In-depth study of this mechanism holds promise for providing novel ideas and strategies for the treatment of hepatocellular carcinoma. Olaparib, as a poly (ADP ribose) polymerase

Table I. Overview of the role and mechanism of cGAS/STING in colorectal cancer.

First author/s, year	Physiological and pathological processes affected by cGAS/STING	Model	Target	cGAS/STING pathway status	Activated or inactivated in colorectal cancer	(Refs.)
Wang *et al*, 2023	Enhanced the abscopal effect with an increase in cross-presenting DCs and $CD8^+$ tumor-specific T cells	Cells and mice	IFN-I	Doxil stimulated the cGAS/STING axis to exert anticancer effects	cGAS/STING pathway was activated	(33)
Wang *et al*, 2022	Predicted the efficacy of cetuximab in the treatment of metastatic colorectal cancer	Blood samples of patients	IFNB1	Patients with STING rs1131769 exhibited shorter overall survival	STING pathway was activated	(9)
Chen *et al*, 2023	Promoted anticancer immunity by maintaining redox homeostasis in colorectal cancer	Database analysis	GPX4	Facilitated anticancer immunity via STING activation	STING pathway was activated	(34)
Mata-Garrido *et al*, 2023	Protected the nuclear membrane and genomic integrity	Colon cancer cells	HP1γ	HP1γ prevented activation of the cGAS/STING pathway	cGAS/STING pathway was activated	(35)
Wei *et al*, 2021	Suppressed DNA repair and enhanced anticancer immunity	Cells and mice	SHP2 and PARP1	Activated the STING pathway to mediate antitumor immunity	STING pathway was activated	(37)
Wang *et al*, 2023	Enhanced immunotherapy for colorectal cancer	The Cancer Genome Atlas public data and mice	BANF1	BANF1 knockout activated the antitumor response mediated by the cGAS/STING pathway	cGAS/STING pathway was activated	(38)
Kunac *et al*, 2022	cGAS/STING was positively associated with MSI-H colorectal cancer	Patients with colorectal cancer	/	cGAS/STING pathway was activated in colorectal cancer cells	cGAS/STING pathway was activated	(39)
Vornholz *et al*, 2023	Sensitized resistant cancers to immune checkpoint inhibitors	Patients with colorectal cancer, mice and cells	IFN signaling	cGAS-STING signaling triggered by genomic instability	cGAS/STING pathway was activated	(40)
Wu *et al*, 2023	Enhanced the therapeutic sensitivity of HER2-positive colon cancer	Cells and mice	HER2/MMAE conjugate RC48	RC48 enhanced the sensitivity of HER2-positive colon cancer cells to immunotherapy by triggering the cGAS/STING pathway	cGAS/STING pathway was activated	(32)
Catalano *et al*, 2020	Clarified that risk alleles serve an important role in colorectal cancer carcinogenesis	Patients with colorectal cancer	IKKε-TBK1-IFN	Activation status of the cGAS/STING pathway was associated with the risk of colorectal cancer	cGAS/STING pathway was activated	(42)
Tian *et al*, 2021	Enhanced the therapeutic effect of 5-fluorouracil	Mice, cells and patients with colorectal cancer	IFN	Anticancer immunity triggered by the activation of STING	STING pathway was activated	(43)

Table I. Continued.

First author/s, year	Physiological and pathological processes affected by cGAS/STING	Model	Target	cGAS/STING pathway status	Activated or inactivated in colorectal cancer	(Refs.)
Liang *et al*, 2023	Regulated the efficacy of anti-PD-1 therapy	Cells and mice	SIX4	cGAS/STING pathway was activated in colorectal cancer cells	cGAS/STING pathway was activated	(44)
Yang *et al*, 2024	Sensitized mice to immune checkpoint blockade immunotherapy	Mice	SN38/TBK1/IRF3	Activated the STING pathway to mediate antitumor immunity	cGAS/STING pathway was activated	(45)
Morehead *et al*, 2023	Increased response to immune checkpoint inhibitors	Cells and mice	MHC-I and PD-L1	Activated the STING pathway to mediate antitumor immunity	STING pathway was activated	(46)
Xia *et al*, 2023	Inhibited both local residual and distant tumors	Mice	/	Photothermal ablation-induced hyperthermia served a crucial role in initiating the cGAS/STING pathway	cGAS/STING pathway was activated	(47)
Hu *et al*, 2021	Defended the integrity of the intestinal mucosa	Cells and mice	STAT3	Deletion of cGAS exacerbated chemical-induced colitis and colitis-associated colon cancer	cGAS pathway was inactivated	(36)
Zheng *et al*, 2023	Inhibited colorectal cancer progression	Cells and mice	KDM5	Suppressed STING promoted cancer immune escape	STING pathway was inactivated	(41)

BANF1, barrier to autointegration nuclear assembly factor 1; cGAS, cyclic GMP-AMP synthase; DC, dendritic cell; GPX4, glutathione peroxidase 4; HP1γ, heterochromatin protein 1γ; IRF3, interferon regulatory factor 3; KDM5, lysine demethylase 5; MHC-I, major histocompatibility complex I; MMAE, monomethyl auristatin E; MSI-H, high microsatellite instability; PARP1, poly(ADP-ribose) polymerase 1; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SHP2, SH2 domain-containing tyrosine phosphatase 2; SIX4, SIX homeobox 4; STING, stimulator of interferon genes; TBK1, TANK binding kinase 1.

Table II. Overview of the role and mechanism of cGAS/STING in liver cancer.

First author/s, year	Physiological and pathological processes affected by cGAS/STING	Model	Target	cGAS/STING pathway status	Activated or inactivated in liver cancer	(Refs.)
Li *et al*, 2022	Improved the response rates of patients with hepatocellular carcinoma to PD-1 Ab	Cells and mice	HIF-1α/IFN-I/NF-κB	Activated the STING pathway to mediate the antitumor effect	STING pathway was activated	(51)
Wang *et al*, 2022	Triggered ER stress-induced apoptosis and mediated anticancer immunity	Cells, mice and GEO database	STAT3	Activated the STING pathway to enhance the anticancer effect of $CD8^+$ T and NK cells	STING pathway was activated	(52)
Ma *et al*, 2023	Caused persistent DNA damage and induced tumor immunosuppression and T-lymphocyte infiltration	Cells and mice pathway was activated	BRCA1/PALB2	Activated the cGAS/STING pathway to induce tumor immunosuppression and T lymphocyte infiltration	cGAS/STING	(53)
Du *et al*, 2024	Induced immunogenic cell death	Cells and mice	/	Pyroptosis-boosted cGAS/STING activation affected the efficiency of liver cancer immunotherapy	cGAS/STING pathway was activated	(54)
Li *et al*, 2022	Defended the integrity of the intestinal mucosa	Patients with cancer, mice and cells	IFN-I and cyclic-di-AMP	Anticancer immunity triggered by the activation of STING	STING pathway was activated	(55)
Cao *et al*, 2023	Effective treatment of residual liver cancer after iRFA	Cells and mice	IFN-I/pIRF3/TNF-α	Induced an anticancer immunity by activating the STING pathway	STING pathway was activated	(56)
Sheng *et al*, 2020	Enhanced the antitumor activity of radiotherapy and immune checkpoint inhibitors	Cells and mice	IFN-γ/PD-L1/GMP-AMP	Induced anticancer immunity by activating the STING pathway	STING pathway was activated	(57)
Xu *et al*, 2024	Enhanced the activity of NK cells within hepatocellular carcinoma	Patients with hepatocellular carcinoma, mice and cells	eEF2K	Induced anticancer immunity by activating the STING pathway	STING pathway was activated	(60)
Sun *et al*, 2023	Induced $CD8^+$ T-cell activation	Cells and mice	rgFlu/PD-L1	Activated the cGAS/STING pathway to exert anticancer effects	cGAS/STING pathway was activated	(61)
Chen *et al*, 2024	Activated the immune microenvironment in reprogramming abscopal tumors	Cells and mice pathway was activated	CXCL9, CXCL10, CXCL11 and CCL5	Activated the cGAS/STING pathway to exert anticancer effects	cGAS/STING	(63)
Qi *et al*, 2020	Served as prognostic biomarkers and immunotherapy targets for liver cancer	Database	LCK, LYN, PIKK, ATM, ATR, MAPK1	Expression of cGAS/STING members in hepatocellular carcinoma tissues was upregulated	cGAS/STING pathway was activated	(65)

Table II. Continued.

First author/s, year	Physiological and pathological processes affected by cGAS/STING	Model	Target	cGAS/STING pathway status	Activated or inactivated in liver cancer	(Refs.)
Li *et al*, 2024	Promoted immunogenic cell death	Patients with hepatocellular carcinoma, mice and cells	IFN and PD-L1	Arsenic trioxide induced immunogenic cell death by activating the cGAS/STING pathway	cGAS/STING pathway was activated	(49)
Sun *et al*, 2024	Enhanced the effect of OK-432 for liver cancer	Cells and mice	TLR4/TBK1/IRF3	Radiofrequency hyperthermia activated cGAS/STING to enhance the efficacy of liver cancer treatment	cGAS/STING pathway was activated	(67)
Lv *et al*, 2024	Mediated the vascular normalization and anticancer immune response	Database, patients with liver cancer, mice and cells	TET2/IL-2/STAT5A	Activated the cGAS/STING pathway to regulate anticancer effects	cGAS/STING pathway was activated	(69)
Du *et al*, 2022	Enhances hepatocellular carcinoma immunotherapy	Patients with liver cancer, mice and cells	TBK1/IRF3	Induced an anticancer immunity by activating the cGAS/STING pathway	cGAS/STING pathway was activated	(71)
Hong *et al*, 2024	Reduced the radiosensitivity of hepatocellular carcinoma	Patients with hepatocellular carcinoma, mice and cells	RECQL4	Induced cancer immune awakening by suppressing the cGAS/STING pathway	cGAS/STING pathway was inactivated	(58)
Thomsen *et al*, 2020	Affected the development of hepatocellular carcinoma	Cells and mice	STAT1/PD-L1/IFN	STING deficiency promoted the progression of advanced liver cancer	STING pathway was inactivated	(59)
Fu *et al*, 2024	Promoted the development of liver cancer	Patients with hepatocellular carcinoma, mice and cells	IDI1/TBK1/IRF3	cGAS/STING pathway was inhibited	cGAS/STING pathway was inactivated	(62)
Zhao *et al*, 2022	Inhibited immune stress in liver cancer cells under hypoxic conditions	Database, cells and patient tissues	RNASEH2A/HIF-2α	Limited activation of cGAS/STING	cGAS/STING pathway was inactivated	(64)
Ma *et al*, 2024	Inhibited the progression of hepatocellular carcinoma	Patients with hepatocellular carcinoma, mice and cells	cGAMP/PI3K/AKT/mTORC1	cGAS was downregulated in hepatocellular carcinoma tissues	cGAS pathway was inactivated	(66)
Wang *et al*, 2022	Promoted the activation of NK cells in liver cancer	Patients with liver cancer, mice and cells	CD47	Antitumor effects of CD47 blockade could be abolished by cGAS/STING inhibition	cGAS/STING pathway was inactivated	(68)

Table II. Continued.

First author/s, year	Physiological and pathological processes affected by cGAS/STING	Model	Target	cGAS/STING pathway status	Activated or inactivated in liver cancer	(Refs.)
Su *et al*, 2023	Promoted the development of liver cancer	Patients with liver cancer, mice and cells	TAK1	Inhibition of macrophage STING may represent a novel therapeutic approach	STING pathway was inactivated	(70)

Ab, antibody; ATM, ATM serine/threonine kinase; ATR, ATR serine/threonine kinase; CCL5, C-C motif chemokine ligand 5; cGAMP, cyclic guanosine monophosphate-adenosine monophosphate; cGAS, cyclic GMP-AMP synthase; CXCL, C-X-C motif chemokine ligand; eEF2K, eukaryotic elongation factor 2 kinase; ER, endoplasmic reticulum; GEO, Gene Expression Omnibus; HIF, hypoxia-inducible factor; IDI1, isopentenyl-diphosphate δ isomerase 1; IRF3, interferon regulatory factor 3; iRFA, incomplete radiofrequency ablation; NK, natural killer; PALB2, partner and localizer of BRCA2; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PIKK, phosphatidylinositol 3-kinase-related kinase; pIRF3, phosphorylated IRF3; RECQL4, RecQ like helicase 4; RNASEH2A, ribonuclease H2 subunit A; STING, stimulator of interferon genes; TAK1, transforming growth factor-β-activated kinase 1; TBK1, TANK binding kinase 1; TET2, tet methylcytosine dioxygenase 2; TLR4, toll like receptor 4.

inhibitor, has been shown to promote radiation-mediated systemic anticancer effects by activating the STING chemokine pathway in hepatocellular carcinoma (63). Hypoxia is one of the characteristics of solid tumors, including hepatocellular carcinoma (64). Hypoxia-induced ribonuclease H2 subunit A inhibits the activation of the cGAS/STING pathway and could predict the prognosis of liver cancer (64). The activation of the cGAS/STING pathway is strongly associated with various immune biomarker sets in hepatocellular carcinoma (65). These findings suggest that members of the cGAS/STING pathway could serve as prognostic biomarkers and immunotherapy targets for hepatocellular carcinoma. Arsenic trioxide has become an effective cytotoxic drug for the treatment of solid tumors, including liver cancer (49). The cGAS/STING/IFN pathway is induced by arsenic trioxide, which enhances immunogenic cell death in hepatocellular carcinoma (49). In clinical hepatocellular carcinoma tissues, cGAS has been demonstrated to be downregulated, and its dysregulation leads to the progression of hepatocellular carcinoma (66). In cellular and animal models, cGAS has been shown to inhibit the progression of hepatocellular carcinoma by suppressing the PI3K/AKT/mTORC1 pathway (66). Radiofrequency ablation has been used as an alternative to surgical treatment for early hepatocellular carcinoma (67). Radiofrequency hyperthermia could enhance the therapeutic effect of OK-432 on liver cancer by enhancing the activity of the cGAS/STING pathway (67). The blockade of CD47 enhanced the capacity of $CD103^+$ dendritic cells to uptake cancer DNA, resulting in the stimulation of the cGAS/STING axis (68). Consequently, this enhancement promoted the activation of NK cells in hepatocellular carcinoma (68). tet methylcytosine dioxygenase 2-mediated cGAS-induced STING activation is required to regulate vascular remodeling and anticancer immune effects in hepatocellular carcinoma (69). Hepatocellular ferroptosis-induced DNA oxidative damage promotes the increase of STING activity in macrophages, thereby promoting the occurrence and development of liver injury and liver cancer (70). Du *et al* (71) identified an immune-cloaking mechanism, specifically the cGAS/STING pathway, which was activated by radiation therapy. Furthermore, their findings suggest that radiation therapy augments the efficacy of immunotherapy for hepatocellular carcinoma.

cGAS/STING pathway regulates the occurrence and progress of pancreatic cancer. Pancreatic cancer is one of the major causes of cancer-related deaths worldwide, reportedly ranking fourth, and effective treatment options are limited (72). There are several treatment strategies for pancreatic cancer, including surgical intervention, immunotherapy, radiotherapy, chemotherapy, targeted therapy or their combination; however, the effect is not satisfactory (72-74). The cGAS/STING signal is considered to serve a crucial regulatory role in the immune response and immunotherapy of malignant tumors (72-77). Therapies targeting cGAS/STING have been applied for the treatment of pancreatic cancer by promoting the immune responses against malignancy through different strategies, either as a monotherapy or in combination with other immunotherapies for pancreatic cancer (11). This section summarizes the progress regarding the role of cGAS/STING in the

occurrence, progress and treatment of pancreatic cancer, and suggests improved strategies for the treatment of pancreatic cancer.

The therapeutic effect of disulfiram and chemoimmunotherapy is enhanced by inhibiting PARP1 expression and activating the cGAS/STING pathway in pancreatic cancer (72). Ectonucleotidase CD73 inhibits the cGAS/STING pathway and cooperates with CD39 to promote the occurrence of pancreatic cancer (73). POLQ is a key mediator in the microhomology-mediated end joining pathway and is crucial for the double-strand break repair of BRCA2 defect type pancreatic cancer (74). POLQ inhibition triggers the immune response in homologous recombination-deficient pancreatic cancer via cGAS/STING signaling (74). The cGAS/STING pathway and cancer-associated fibroblasts serve a pivotal role in overcoming the cancer-associated fibroblast barrier and promoting immune cell infiltration in pancreatic cancer (75). Activation of the cGAS/STING pathway results in the upregulation of dual oxidase 2, as well as increased expression of hypoxia-inducible factor-1α (HIF-1α) and VEGF-A, normoxic expression of HIF-1α and VEGF-A, and DNA double strand cleavage (76). These findings suggest that cGAS/STING signaling may contribute to the development of an oxidative and pro-angiogenic microenvironment, potentially leading to genetic instability associated with inflammation in pancreatic cancer. The silencing of deltex E3 ubiquitin ligase 3L (DTX3L) leads to enhanced activation of the cGAS/STING pathway and improves the immune antitumor effect in pancreatic cancer (77). A novel promising treatment method for pancreatic cancer may be a strategy based on the DTX3L/cGAS/STING axis (77).

Due to extensive evidence indicating that the cGAS/STING pathway regulates immune cells in the cancer microenvironment, biological therapies based on cGAS/STING have attracted widespread attention (72-77). Pancreatic cancer and other cancer types have special tumor microenvironments. Researchers have conducted in-depth research on them and found that cGAS/STING serves a crucial role in the progression of pancreatic cancer and in developing effective strategies. cGAS/STING-based therapies have also been shown to work in combination with other therapies, such as immune checkpoints, vaccines and immune cell-targeting nanoparticles. Although the present review aims to summarize the role of cGAS/STING signaling in pancreatic cancer, in-depth investigations are still required to clarify the various mechanisms by which STING may be activated and to develop improved therapeutic approaches and drugs to enhance the clinical care of patients with pancreatic cancer.

3. Conclusion and future perspective

The early symptoms of most patients with gastrointestinal cancer are not obvious and non-specific, and are easy to overlook, and there are no good specific and effective early diagnostic markers for clinical diagnosis (2). It is necessary to elucidate the pathogenesis of gastrointestinal tumors and to find more effective diagnostic and treatment strategies, as gastrointestinal cancer is often diagnosed in the advanced stage. Increasing evidence suggests that cGAS/STING is closely related to the occurrence, progression and treatment of gastrointestinal cancer. Targeting the cGAS/STING pathway is a promising approach for the treatment of gastrointestinal cancer. Combining cGAS/STING pathway-based therapeutic interventions with traditional chemotherapy, targeted therapy or immunotherapy may be a commonly used and effective strategy to treat gastrointestinal tumors. However, the exact molecular mechanism of the cGAS/STING signaling pathway in gastrointestinal cancer has not been fully revealed, and the safety of treatment methods based on the cGAS/STING pathway also needs to be comprehensively evaluated. Future translational research and clinical trials necessitate the advancement of therapeutic strategies based on the cGAS/STING pathway. Subsequent research involves elucidating the molecular mechanisms and downstream targets, evaluating safety and therapeutic efficacy, and exploring the potential of combining cGAS/STING-based therapies with multiple treatment modalities. Ultimately, such endeavors may be an effective way to overcome gastrointestinal tumors and reduce the social and patient burden.

In cancer, cancer-derived DNA, oncogenic viruses, exosomes and DNA damage caused by radiotherapy can activate the cGAS/STING pathway, thereby inducing cellular senescence, inflammation and antitumor immunity. By contrast, CEA and CA19-9 reflect the presence and progression of cancer through blood tests (78-80). Although there are differences in their mechanisms of action, the cGAS/STING pathway, CEA and CA19-9 can all serve as important tools for the detection and treatment of gastrointestinal cancers. Delving deeply into the mechanisms underlying the role of the cGAS/STING pathway in the initiation and progression of gastrointestinal cancer, as well as its application prospects in cancer immunotherapy and radiotherapy can offer novel insights into the diagnosis and treatment of gastrointestinal cancer. Investigating the interaction between the cGAS/STING pathway and clinical biomarkers such as CEA and CA19-9, may provide a theoretical basis for the development of more precise and effective detection and treatment methods for gastrointestinal cancer. In the future, by integrating the detection results of the cGAS/STING pathway with clinical biomarkers such as CEA and CA19-9, a more comprehensive risk assessment model for gastrointestinal cancer can be established, which can offer patients more personalized treatment plans and prognosis evaluations.

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Authors' contributions

ZL and JJ designed the research. CL, LT, WY and YG analyzed data. ZL, CL, WX and JJ contributed to the writing and revisions. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Wang S, Zheng R, Li J, Zeng H, Li L, Chen R, Sun K, Han B, Bray F, Wei W and He J: Global, regional, and national lifetime risks of developing and dying from gastrointestinal cancers in 185 countries: A population-based systematic analysis of GLOBOCAN. Lancet Gastroenterol Hepatol 9: 229-237, 2024.
2. Wang T, Jin Y, Wang M, Chen B, Sun J, Zhang J, Yang H, Deng X, Cao X, Wang L and Tang Y: SALL4 in gastrointestinal tract cancers: Upstream and downstream regulatory mechanisms. Mol Med 30: 46, 2024.
3. Samson N and Ablasser A: The cGAS-STING pathway and cancer. Nat Cancer 3: 1452-1463, 2022.
4. Lv H, Zong Q, Chen C, Lv G, Xiang W, Xing F, Jiang G, Yan B, Sun X, Ma Y, *et al*: TET2-mediated tumor cGAS triggers endothelial STING activation to regulate vasculature remodeling and anti-tumor immunity in liver cancer. Nat Commun 15: 6, 2024.
5. Wang Y, Luo J, Alu A, Han X, Wei Y and Wei X: cGAS-STING pathway in cancer biotherapy. Mol Cancer 19: 136, 2020.
6. Canesso MCC, Lemos L, Neves TC, Marim FM, Castro TBR, Veloso ÉS, Queiroz CP, Ahn J, Santiago HC, Martins FS, *et al*: The cytosolic sensor STING is required for intestinal homeostasis and control of inflammation. Mucosal Immunol 11: 820-834, 2018.
7. Ke X, Hu T and Jiang M: cGAS-STING signaling pathway in gastrointestinal inflammatory disease and cancers. FASEB J 36: e22029, 2022.
8. Li Y, Chen H, Yang Q, Wan L, Zhao J, Wu Y, Wang J, Yang Y, Niu M, Liu H, *et al*: Increased Drp1 promotes autophagy and ESCC progression by mtDNA stress mediated cGAS-STING pathway. J Exp Clin Cancer Res 41: 76, 2022.
9. Wang J, Xiao Y, Loupakis F, Stintzing S, Yang Y, Arai H, Battaglin F, Kawanishi N, Jayachandran P, Soni S, *et al*: Genetic variants involved in the cGAS-STING pathway predict outcome in patients with metastatic colorectal cancer: Data from FIRE-3 and TRIBE trials. Eur J Cancer 172: 22-30, 2022.
10. Xu D, Tian Y, Xia Q and Ke B: The cGAS-STING Pathway: Novel Perspectives in Liver Diseases. Front Immunol 12: 682736, 2021.
11. Mohseni G, Li J, Ariston Gabriel AN, Du L, Wang YS and Wang C: The Function of cGAS-STING Pathway in Treatment of Pancreatic Cancer. Front Immunol 12: 781032, 2021.
12. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
13. Xu Y, Han J, Zhang X, Zhang X, Song J, Gao Z, Qian H, Jin J and Liang Z: Exosomal circRNAs in gastrointestinal cancer: Role in occurrence, development, diagnosis and clinical application (Review). Oncol Rep 51: 19, 2024.
14. Lu L, Gao Z, Jin L, Geng H and Liang Z: Novel role of circRNAs in the drug resistance of gastric cancer: regulatory mechanisms and future for cancer therapy. Front Pharmacol 15: 1435264, 2024.
15. Shen Q, Yang L, Li C, Wang T, Lv J, Liu W, Lin Y, Yin Y and Tao K: Metformin promotes cGAS/STING signaling pathway activation by blocking AKT phosphorylation in gastric cancer. Heliyon 9: e18954, 2023.
16. Li C, Shen Q, Zhang P, Wang T, Liu W, Li R, Ma X, Zeng X, Yin Y and Tao K: Targeting MUS81 promotes the anticancer effect of WEE1 inhibitor and immune checkpoint blocking combination therapy via activating cGAS/STING signaling in gastric cancer cells. J Exp Clin Cancer Res 40: 315, 2021.
17. Yuan M, Guo XL, Chen JH, He Y, Liu ZQ, Zhang HP, Ren J and Xu Q: Anlotinib suppresses proliferation, migration, and immune escape of gastric cancer cells by activating the cGAS-STING/IFN-beta pathway. Neoplasma 69: 807-819, 2022.
18. Yang KS, Xu CQ and Lv J: Identification and validation of the prognostic value of cyclic GMP-AMP synthase-stimulator of interferon (cGAS-STING) related genes in gastric cancer. Bioengineered 12: 1238-1250, 2021.
19. Fukai S, Nakajima S, Saito M, Saito K, Kase K, Nakano H, Sato T, Sakuma M, Kaneta A, Okayama H, *et al*: Down-regulation of stimulator of interferon genes (STING) expression and $CD8^+$ T-cell infiltration depending on HER2 heterogeneity in HER2-positive gastric cancer. Gastric Cancer 26: 878-890, 2023.
20. Duan Y, Li S, Huang B, Dou Y, Kong P, Kang W and Xu D: CD47-targeted immunotherapy unleashes antitumour immunity in Epstein-Barr virus-associated gastric cancer. Clin Immunol 247: 109238, 2023.
21. Hosseinzadeh S, Imani M, Pourfarzi F, Jafari N, AbedianKenari S and Safarzadeh E: Combination of IFN-gamma with STING agonist and PD-1 immune checkpoint blockade: A potential immunotherapy for gastric cancer. Med Oncol 41: 110, 2024.
22. Liang L, Chai Y, Chai F, Liu H, Ma N, Zhang H, Zhang S, Nong L, Li T and Zhang B: Expression of SASP, DNA damage response, and cell proliferation factors in early gastric neoplastic lesions: Correlations and clinical significance. Pathol Oncol Res 28: 1610401, 2022.
23. Esophageal Cancer Treatment (PDQ(R)): Health Professional Version. In: PDQ Cancer Information Summaries, Bethesda (MD), 2002.
24. Li Y, Yang Q, Chen H, Yang X, Han J, Yao X, Wei X, Si J, Yao H, Liu H, *et al*: TFAM downregulation promotes autophagy and ESCC survival through mtDNA stress-mediated STING pathway. Oncogene 41: 3735-3746, 2022.
25. Nakajima S, Mimura K, Kaneta A, Saito K, Katagata M, Okayama H, Saito M, Saze Z, Watanabe Y, Hanayama H, *et al*: Radiation-induced remodeling of the tumor microenvironment through tumor cell-intrinsic expression of cGAS-STING in esophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 115: 957-971, 2023.
26. Matsuishi A, Nakajima S, Kaneta A, Saito K, Fukai S, Sakuma M, Tsumuraya H, Okayama H, Saito M, Mimura K, *et al*: The tumor cell-intrinsic cGAS-STING pathway is associated with the high density of $CD8^+$ T cells after chemotherapy in esophageal squamous cell carcinoma. Esophagus 21: 165-175, 2024.
27. Nakajima S, Mimura K, Kaneta A, Katagata M, Okayama H, Saito M, Saze Z, Hanayama H, Tada T, Momma T and Kono K: Remodeling of the tumor microenvironment by radiotherapy through the cGAS-STING pathway in esophageal squamous cell carcinoma. Gan To Kagaku Ryoho 50: 1099-1101, 2023 (In Japanese).
28. Li J, Ko JM, Dai W, Yu VZ, Ng HY, Hoffmann JS and Lung ML: Depletion of DNA polymerase theta inhibits tumor growth and promotes genome instability through the cGAS-STING-ISG pathway in esophageal squamous cell carcinoma. Cancers (Basel) 13: 3204, 2021.
29. Du J, Kageyama SI, Yamashita R, Hirata H, Hakozaki Y, Okumura M, Motegi A, Hojo H, Nakamura M, Hirano Y, *et al*: Impacts of the STING-IFNAR1-STAT1-IRF1 pathway on the cellular immune reaction induced by fractionated irradiation. Cancer Sci 113: 1352-1361, 2022.
30. Li X, Liu H, Gao W, Yang Q, Li X, Zhou X, Wang L, Lu Z, Liu J, Luo A, *et al*: Octadecyl Gallate and Lipid-modified $MnSe_2$ nanoparticles enhance radiosensitivity in esophageal squamous cell carcinoma and promote radioprotection in normal tissues. Adv Mater 36: e2311291, 2024.
31. Xia C, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N and Chen W: Cancer statistics in China and United States, 2022: Profiles, trends, and determinants. Chin Med J (Engl) 135: 584-590, 2022.

32. Wu X, Xu L, Li X, Zhou Y, Han X, Zhang W, Wang W, Guo W, Liu W, Xu Q and Gu Y: A HER2-targeting antibody-MMAE conjugate RC48 sensitizes immunotherapy in HER2-positive colon cancer by triggering the cGAS-STING pathway. Cell Death Dis 14: 550, 2023.
33. Wang L, Luo R, Onyshchenko K, Rao X, Wang M, Menz B, Gaedicke S, Grosu AL, Firat E and Niedermann G: Adding liposomal doxorubicin enhances the abscopal effect induced by radiation/αPD1 therapy depending on tumor cell mitochondrial DNA and cGAS/STING. J Immunother Cancer 11: e006235, 2023.
34. Chen B, Hong Y, Zhai X, Deng Y, Hu H, Tian S, Zhang Y, Ren X, Zhao J and Jiang C: m6A and m5C modification of GPX4 facilitates anticancer immunity via STING activation. Cell Death Dis 14: 809, 2023.
35. Mata-Garrido J, Frizzi L, Nguyen T, He X, Chang-Marchand Y, Xiang Y, Reisacher C, Casafont I and Arbibe L: HP1γ prevents activation of the cGAS/STING pathway by preserving nuclear envelope and genomic integrity in colon adenocarcinoma cells. Int J Mol Sci 24: 7347, 2023.
36. Hu S, Fang Y, Chen X, Cheng T, Zhao M, Du M, Li T, Li M, Zeng Z, Wei Y, *et al*: cGAS restricts colon cancer development by protecting intestinal barrier integrity. Proc Natl Acad Sci USA 118: e2105747118, 2021.
37. Wei B, Xu L, Guo W, Wang Y, Wu J, Li X, Cai X, Hu J, Wang M, Xu Q, *et al*: SHP2-mediated inhibition of DNA repair contributes to cGAS-STING activation and chemotherapeutic sensitivity in colon cancer. Cancer Res 81: 3215-3228, 2021.
38. Wang M, Huang Y, Chen M, Wang W, Wu F, Zhong T, Chen X, Wang F, Li Y, Yu J, *et al*: Inhibition of tumor intrinsic BANF1 activates antitumor immune responses via cGAS-STING and enhances the efficacy of PD-1 blockade. J Immunother Cancer 11: e007035, 2023.
39. Kunac N, Degoricija M, Viculin J, Omerović J, Terzić J, Vilović K and Korac-Prlic J: Activation of cGAS-STING pathway is associated with MSI-H stage IV colorectal cancer. Cancers (Basel) 15: 221, 2022.
40. Vornholz L, Isay SE, Kurgyis Z, Strobl DC, Loll P, Mosa MH, Luecken MD, Sterr M, Lickert H, Winter C, *et al*: Synthetic enforcement of STING signaling in cancer cells appropriates the immune microenvironment for checkpoint inhibitor therapy. Sci Adv 9: eadd8564, 2023.
41. Zheng H, Wu L, Xiao Q, Meng X, Hafiz A, Yan Q, Lu R and Cao J: Epigenetically suppressed tumor cell intrinsic STING promotes tumor immune escape. Biomed Pharmacother 157: 114033, 2023.
42. Catalano C, da Silva Filho MI, Frank C, Lu S, Jiraskova K, Vymetalkova V, Levy M, Liska V, Vycital O, Naccarati A, *et al*: Epistatic effect of TLR3 and cGAS-STING-IKKepsilon-TBK1-IFN signaling variants on colorectal cancer risk. Cancer Med 9: 1473-1484, 2020.
43. Tian J, Zhang D, Kurbatov V, Wang Q, Wang Y, Fang D, Wu L, Bosenberg M, Muzumdar MD, Khan S, *et al*: 5-Fluorouracil efficacy requires anti-tumor immunity triggered by cancer-cell-intrinsic STING. EMBO J 40: e106065, 2021.
44. Liang B, Zhang EH, Ye Z, Storts H, Jin W, Zheng X, Hylton H, Zaleski O, Xing X, Miles W and Wang JJ: SIX4 controls Anti-PD-1 efficacy by regulating STING expression. Cancer Res Commun 3: 2412-2419, 2023.
45. Yang Y, Qi J, Hu J, Zhou Y, Zheng J, Deng W, Inam M, Guo J, Xie Y, Li Y, *et al*: Lovastatin/SN38 co-loaded liposomes amplified ICB therapeutic effect via remodeling the immunologically-cold colon tumor and synergized stimulation of cGAS-STING pathway. Cancer Lett 588: 216765, 2024.
46. Morehead LC, Garg S, Wallis KF, Simoes CC, Siegel ER, Tackett AJ and Miousse IR: Increased response to immune checkpoint inhibitors with dietary methionine restriction in a colorectal cancer model. Cancers 15: 4467, 2023.
47. Xia J, Wang L, Shen T, Li P, Zhu P, Xie S, Chen Z, Zhou F, Zhang J, Ling J, *et al*: Integrated manganese (III)-doped nanosystem for optimizing photothermal ablation: Amplifying hyperthermia-induced STING pathway and enhancing antitumor immunity. Acta Biomater 155: 601-617, 2023.
48. Ma J, Xin Y, Wang Q and Ding L: Roles of cGAS-STING pathway in radiotherapy combined with immunotherapy for hepatocellular carcinoma. Mol Cancer Ther 23: 447-453, 2024.
49. Li X, Pan YF, Chen YB, Wan QQ, Lin YK, Shang TY, Xu MY, Jiang TY, Pei MM, Tan YX, *et al*: Arsenic trioxide augments immunogenic cell death and induces cGAS-STING-IFN pathway activation in hepatocellular carcinoma. Cell Death Dis 15: 300, 2024.
50. Chen B, Rao X, Wang X, Luo Z, Wang J, Sheng S, Liu Y, Zhang N, Jin S, Chen H, *et al*: cGAS-STING signaling pathway and liver disease: From basic research to clinical practice. Front Pharmacol 12: 719644, 2021.
51. Li K, Gong Y, Qiu D, Tang H, Zhang J, Yuan Z, Huang Y, Qin Y, Ye L and Yang Y: Hyperbaric oxygen facilitates Teniposide-induced cGAS-STING activation to enhance the antitumor efficacy of PD-1 antibody in HCC. J Immunother Cancer 10: e004006, 2022.
52. Wang X, Hu R, Song Z, Zhao H, Pan Z, Feng Y, Yu Y, Han Q and Zhang J: Sorafenib combined with STAT3 knockdown triggers ER stress-induced HCC apoptosis and cGAS-STING-mediated anti-tumor immunity. Cancer Lett 547: 215880, 2022.
53. Ma H, Kang Z, Foo TK, Shen Z and Xia B: Disrupted BRCA1-PALB2 interaction induces tumor immunosuppression and T-lymphocyte infiltration in HCC through cGAS-STING pathway. Hepatology 77: 33-47, 2023.
54. Du Q, Luo Y, Xu L, Du C, Zhang W, Xu J, Liu Y, Liu B, Chen S, Wang Y, *et al*: Smart responsive Fe/Mn nanovaccine triggers liver cancer immunotherapy via pyroptosis and pyroptosis-boosted cGAS-STING activation. J Nanobiotechnol 22: 95, 2024.
55. Li Z, Zhang Y, Hong W, Wang B, Chen Y, Yang P, Zhou J, Fan J, Zeng Z and Du S: Gut microbiota modulate radiotherapy-associated antitumor immune responses against hepatocellular carcinoma Via STING signaling. Gut Microbes 14: 2119055, 2022.
56. Cao Y, Sun T, Sun B, Zhang G, Liu J, Liang B, Zheng C and Kan X: Injectable hydrogel loaded with lysed OK-432 and doxorubicin for residual liver cancer after incomplete radiofrequency ablation. J Nanobiotechnol 21: 404, 2023.
57. Sheng H, Huang Y, Xiao Y, Zhu Z, Shen M, Zhou P, Guo Z, Wang J, Wang H, Dai W, *et al*: ATR inhibitor AZD6738 enhances the antitumor activity of radiotherapy and immune checkpoint inhibitors by potentiating the tumor immune microenvironment in hepatocellular carcinoma. J Immunother Cancer 8: e000340, 2020.
58. Hong W, Zhang Y, Wang S, Li Z, Zheng D, Hsu S, Zhou J, Fan J, Chen Z, Xia X, *et al*: RECQL4 inhibits radiation-induced tumor immune awakening via suppressing the cGAS-STING pathway in hepatocellular carcinoma. Adv Sci (Weinh) 11: e2308009, 2024.
59. Thomsen MK, Skouboe MK, Boularan C, Vernejoul F, Lioux T, Leknes SL, Berthelsen MF, Riedel M, Cai H, Joseph JV, *et al*: The cGAS-STING pathway is a therapeutic target in a preclinical model of hepatocellular carcinoma. Oncogene 39: 1652-1664, 2020.
60. Xu Y, Sun F, Tian Y, Zeng G, Lei G, Bai Z, Wang Y, Ge X, Wang J, Xiao C, *et al*: Enhanced NK cell activation via eEF2K-mediated potentiation of the cGAS-STING pathway in hepatocellular carcinoma. Int Immunopharmacol 129: 111628, 2024.
61. Sun F, Xu Y, Deng Z and Yang P: A recombinant oncolytic influenza virus expressing a PD-L1 antibody induces $CD8^+$ T-cell activation via the cGas-STING pathway in mice with hepatocellular carcinoma. Int Immunopharmacol 120: 110323, 2023.
62. Fu L, Ding H, Bai Y, Cheng L, Hu S and Guo Q: IDI1 inhibits the cGAS-Sting signaling pathway in hepatocellular carcinoma. Heliyon 10: e27205, 2024.
63. Chen G, Zheng D, Zhou Y, Du S and Zeng Z: Olaparib enhances radiation-induced systemic anti-tumor effects via activating STING-chemokine signaling in hepatocellular carcinoma. Cancer Lett 582: 216507, 2024.
64. Zhao F, Liu A, Gong X, Chen H, Wei J, Chen B, Chen S, Yang R, Fan Y and Mao R: Hypoxia-induced RNASEH2A limits activation of cGAS-STING signaling in HCC and predicts poor prognosis. Tumori 108: 63-76, 2022.
65. Qi Z, Yan F, Chen D, Xing W, Li Q, Zeng W, Bi B and Xie J: Identification of prognostic biomarkers and correlations with immune infiltrates among cGAS-STING in hepatocellular carcinoma. Biosci Rep 40: BSR20202603, 2020.
66. Ma D, Yang M, Sun C, Cui X, Xiong G, Wang Q, Jing W, Chen H, Lv X, Liu S, *et al*: cGAS suppresses hepatocellular carcinoma independent of its cGAMP synthase activity. Cell Death Differ 31: 722-737, 2024.
67. Sun B, Zhang Q, Sun T, Liu J, Cao Y, Liang B, Zheng C and Kan X: Radiofrequency hyperthermia enhances the effect of OK-432 for Hepatocellular carcinoma by activating of TLR4-cGAS-STING pathway. Int Immunopharmacol 130: 111769, 2024.

68. Wang S, Wu Q, Chen T, Su R, Pan C, Qian J, Huang H, Yin S, Xie H, Zhou L and Zheng S: Blocking CD47 promotes antitumour immunity through $CD103^+$ dendritic cell-NK cell axis in murine hepatocellular carcinoma model. J Hepatol 77: 467-478, 2022.
69. Lv H, Zong Q, Chen C, Lv G, Xiang W, Xing F, Jiang G, Yan B, Sun X, Ma Y, *et al*: TET2-mediated tumor cGAS triggers endothelial STING activation to regulate vasculature remodeling and anti-tumor immunity in liver cancer. Nat Commun 15: 6, 2024.
70. Su W, Gao W, Zhang R, Wang Q, Li L, Bu Q, Xu Z, Liu Z, Wang M, Zhu Y, Wu G, *et al*: TAK1 deficiency promotes liver injury and tumorigenesis via ferroptosis and macrophage cGAS-STING signalling. JHEP Rep 5: 100695, 2023.
71. Du SS, Chen GW, Yang P, Chen YX, Hu Y, Zhao QQ, Zhang Y, Liu R, Zheng DX, Zhou J, *et al*: Radiation therapy promotes hepatocellular carcinoma immune cloaking via PD-L1 Upregulation induced by cGAS-STING activation. Int J Radiat Oncol Biol Phys 112: 1243-1255, 2022.
72. Huang S, Xie P, Huang X, Chen Z, Yang J, Wang J, Liu C, Li H and Zhou B: Disulfiram combined with chemoimmunotherapy potentiates pancreatic cancer treatment efficacy through the activation of cGAS-STING signaling pathway via suppressing PARP1 expression. Am J Cancer Res 13: 2055-2065, 2023.
73. Jacoberger-Foissac C, Cousineau I, Bareche Y, Allard D, Chrobak P, Allard B, Pommey S, Messaoudi N, McNicoll Y, Soucy G, *et al*: CD73 inhibits cGAS-STING and cooperates with CD39 to promote pancreatic cancer. Cancer Immunol Res 11: 56-71, 2023.
74. Oh G, Wang A, Wang L, Li J, Werba G, Weissinger D, Zhao E, Dhara S, Hernandez RE, Ackermann A, *et al*: POLQ inhibition elicits an immune response in homologous recombination-deficient pancreatic adenocarcinoma via cGAS/STING signaling. J Clin Invest 133: e165934, 2023.
75. Kabashima A, Matsuo Y, Ito S, Akiyama Y, Ishii T, Shimada S, Masamune A, Tanabe M and Tanaka S: cGAS-STING signaling encourages immune cell overcoming of fibroblast barricades in pancreatic cancer. Sci Rep 12: 10466, 2022.
76. Wang SL, Wu Y, Konate M, Lu J, Mallick D, Antony S, Meitzler JL, Jiang G, Dahan I, Juhasz A, *et al*: Exogenous DNA enhances DUOX2 expression and function in human pancreatic cancer cells by activating the cGAS-STING signaling pathway. Free Radic Biol Med 205: 262-274, 2023.
77. Lin S: DTX3L mediated ubiquitination of cGAS suppresses antitumor immunity in pancreatic cancer. Biochem Biophys Res Commun 681: 106-110, 2023.
78. Yousef A, Yousef M, Zeineddine MA, More A, Fanaeian M, Chowdhury S, Knafl M, Edelkamp P, Ito I, Gu Y, *et al*: Serum tumor markers and outcomes in patients with appendiceal adenocarcinoma. JAMA Netw Open 7: e240260, 2024.
79. Li R, Wang J, Xie Z, Tian X, Hou J, Wang D, Qian H, Shen H and Xu W: CircUSP1 as a novel marker promotes gastric cancer progression via stabilizing HuR to upregulate USP1 and Vimentin. Oncogene 43: 1033-1049, 2024.
80. Tian Y, Wang Y, Wen N, Wang S, Li B and Liu G: Prognostic factors associated with early recurrence following liver resection for colorectal liver metastases: A systematic review and meta-analysis. BMC Cancer 24: 426, 2024.