

cGAS-STING pathway in digestive tract cancer: From molecular mechanisms to therapeutic applications (Review)

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Abstract. As a classic cytosolic DNA sensor, the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway contributes to the secretion of multiple inflammatory molecules and functions as a suppressor or promoter in tumor development. Currently, the effect of this pathway on digestive tract cancer types remains unclear, which may be due to its paradoxical roles in different cell types. Tumor cells in digestive cancer often employ multiple mechanisms to inhibit this pathway activation, which then restricts the infiltration of antitumor immune cells and facilitates the formation of an immunosuppressive microenvironment. However, cGAS-STING pathway activation also influences the function of multiple immune cells. For example, while it mainly potentiates the function of dendritic cells and natural killer cells in the tumor microenvironment, it can also promote macrophage polarization into the immunosuppressive M2 subset. To improve the understanding of the cGAS-STING pathway in digestive cancer types, the present article systematically reviews the regulatory mechanism and effects of this pathway across different malignancies of the digestive system, including oral cavity, esophageal, gastric, hepatobiliary, pancreatic and colorectal cancer. Furthermore, the present review examines potential stimulatory strategies

and future directions to utilize this pathway against tumors, such as inducing DNA damage, removing cell-intrinsic inhibitory signals and direct activation by agonists. Overall, the present review aims to provide new perspectives and ideas for leveraging the cGAS-STING pathway to exert antitumor effects by highlighting the changes and roles of this pathway in digestive tract cancer types.

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1. Introduction

Upon identifying cytosolic DNA, cyclic GMP-AMP synthase (cGAS) catalyzes the synthesis of cyclic GMP-AMP (cGAMP), which then initiates stimulator of interferon genes (STING)-related downstream signaling cascades to drive the production of type I interferons (IFNs) and pro-inflammatory mediators (1,2). Therefore, the cGAS-STING pathway mediates antiviral and antitumor immune responses (3,4). However, tumor cells often employ multiple mechanisms to inactivate this pathway to evade immune elimination (5,6).

Digestive tract cancers remain a notable global health burden (7). There is increasing evidence that triggering cGAS-STING signaling may be a promising therapeutic avenue in these cancer types. In gastric cancer (GC) and colorectal cancer (CRC), tumors with deficient mismatch repair (dMMR) exhibit a high tumor mutational burden and increased expression of cGAS and STING (8,9). Moreover, expression levels of cGAS and STING correlate with increased infiltration of immune cells in the tumor microenvironment (TME) (10). Clinically, patients with dMMR GC or CRC benefit more from treatment with immune checkpoint inhibitors (ICIs) compared

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with those with proficient MMR (pMMR) (8,9). The enhanced response to ICIs observed in dMMR patients is closely linked to a higher mutational and neoantigen burden and may also be attributed to increased cGAS-STING pathway activity. Therefore, these reports indicate that the tumor cell-intrinsic cGAS-STING pathway may potentiate immunotherapy efficacy in digestive cancer types.

Notably, cGAS and STING are also expressed in intra-tumoral immune and stromal cells, where they may exert cell type-specific effects (11-13). Therefore, the role of this pathway in digestive tract cancer cannot be inferred from tumor cell-intrinsic signaling alone, and requires further understanding in these tumors (14). This limitation restricts the application of this pathway in cancer therapy. Further investigation may reveal novel therapeutic opportunities to regulate this pathway in digestive cancer.

In the present review, the molecular fundamentals of the cGAS-STING pathway are first briefly summarized. Secondly, the molecular mechanisms by which cancer cells regulate this pathway in oral cavity, esophageal, gastric, hepatobiliary, pancreatic and colorectal cancer are explored. Next, the impact of this pathway on the immune landscapes of these cancer types is explored. Finally, the possible therapeutic strategies and future research directions for utilizing this pathway against digestive cancer are discussed and predicted.

2. Molecular fundamentals of the cGAS-STING pathway

Acting as a pattern recognition receptor system, the cGAS-STING pathway is initiated by recognizing cytosolic DNA (15,16). As illustrated in Fig. 1, upon binding to cytosolic DNA, cGAS can catalyze the synthesis of the second messenger cGAMP from ATP and GTP (17). Subsequently, the STING-cGAMP complex traffics to the Golgi apparatus from the endoplasmic reticulum via coat protein complex II. Upon translocation, STING undergoes a critical conformational shift that enables it to activate TANK-binding kinase 1 (TBK1) and the inhibitor of κ B kinase complex. Activated TBK1 phosphorylates IFN regulatory factor 3 (IRF3), driving the expression of type I IFNs, while also facilitating NF- κ B nuclear translocation to promote the production of pro-inflammatory cytokines (2). Secreted type I IFNs can further induce the expression of IFN-stimulated genes, such as bone marrow stromal antigen 2 and 2'-5'-oligoadenylate synthase 1. The products triggered by this pathway ultimately influence the innate and adaptive immune responses (18). Moreover, cGAMP can induce LC3 lipidation to promote cellular autophagy, which helps clear cytosolic DNA and viral particles (19). This autophagy-mediated response may establish a negative feedback loop to prevent excessive STING signaling.

It has been confirmed that the cGAS-STING pathway can be activated by aberrant cytosolic DNA accumulation derived from intracellular nuclear and mitochondrial DNA, as well as internalized extracellular DNA (20). While the molecular cascade of this pathway is well-defined, the origin of exogenous DNA in the TME is still unclear. Neutrophils, macrophages and eosinophils in the TME can release extracellular traps containing DNA components to influence tumor progression (21,22). Neutrophil extracellular traps (NETs) have been found to activate STING signaling to induce intestinal

barrier dysfunction (23) and promote acute lung injury (24,25). Similar to NETs, macrophage extracellular traps and eosinophil extracellular traps also contain DNA components (26,27). These findings indicate that this pathway may be triggered by extracellular DNA released from these immune cells. Further investigation is necessary to determine whether extracellular trap-related DNA in the TME affects tumor progression by activating this pathway.

3. Roles of cGAS-STING in digestive system cancer types

The activity of the tumor cell-intrinsic cGAS-STING pathway can be regulated by diverse factors, such as radiotherapy, chemotherapy and cell-intrinsic molecules. This complex regulatory network is summarized in Fig. 2. Upon activation, the cGAS-STING pathway modulates the recruitment and function of immune cells within the TME to alter the equilibrium between antitumor and protumor immune responses, ultimately influencing tumor progression (Fig. 3).

Oral cavity cancer

Clinical associations and expression features of the cGAS-STING pathway. Oral squamous cell carcinoma (OSCC) is one of the most diagnosed oral malignancies. Clinically, patients in the cGAS-STING high cluster have a more optimal prognosis than those in the cGAS-STING low cluster (28). *Human papillomavirus* (HPV) infection is an important driver of the oncogenesis of OSCC. Evidence demonstrates that cGAS-STING pathway activity in OSCC is influenced by HPV infection. In HPV⁺ OSCC, HPV16 promotes tumor immune escape via NLR family member X1-mediated STING degradation (29). Therefore, STING expression in HPV16⁺ OSCC is associated with improved disease free survival in these patients (30). These studies indicate that attenuating HPV16-mediated STING degradation or activating this pathway may effectively control the development of HPV16⁺ OSCC. Beyond HPV infection, the out-membrane vesicles derived from *Porphyromonas gingivalis* also inactivate the tumor cell-intrinsic cGAS-STING pathway to promote the immune escape of OSCC by decreasing IL-1 β secretion and limiting the infiltration of natural killer (NK) cells and dendritic cells (DCs) (31).

Tumor cell-intrinsic regulatory mechanisms of the cGAS-STING pathway. Tumor cells employ multiple mechanisms to inhibit the cGAS-STING pathway to promote OSCC progression. Firstly, STING levels are reduced in OSCC. Sex-determining region Y box2 (SOX2) promotes the autophagy-associated degradation of STING in OSCC cells, thereby reducing the type I IFN signaling pathway and inducing the formation of an immunosuppressive TME (32). Secondly, interfering with signal transduction can also inhibit the activity of the cGAS-STING pathway in OSCC. For instance, mutant TP53 contributes to an immunosuppressive TME in OSCC through inhibiting this pathway (33) and can bind to TBK1 to disrupt the transduction of cGAS-STING signaling in precancerous epithelial cells, resulting in increased regulatory T cell (Treg) infiltration and the tumorigenesis of OSCC (34). Additionally, by maintaining mitochondrial homeostasis, casein kinase 2 interacting protein 1, upregulated in OSCC, can upregulate the expression

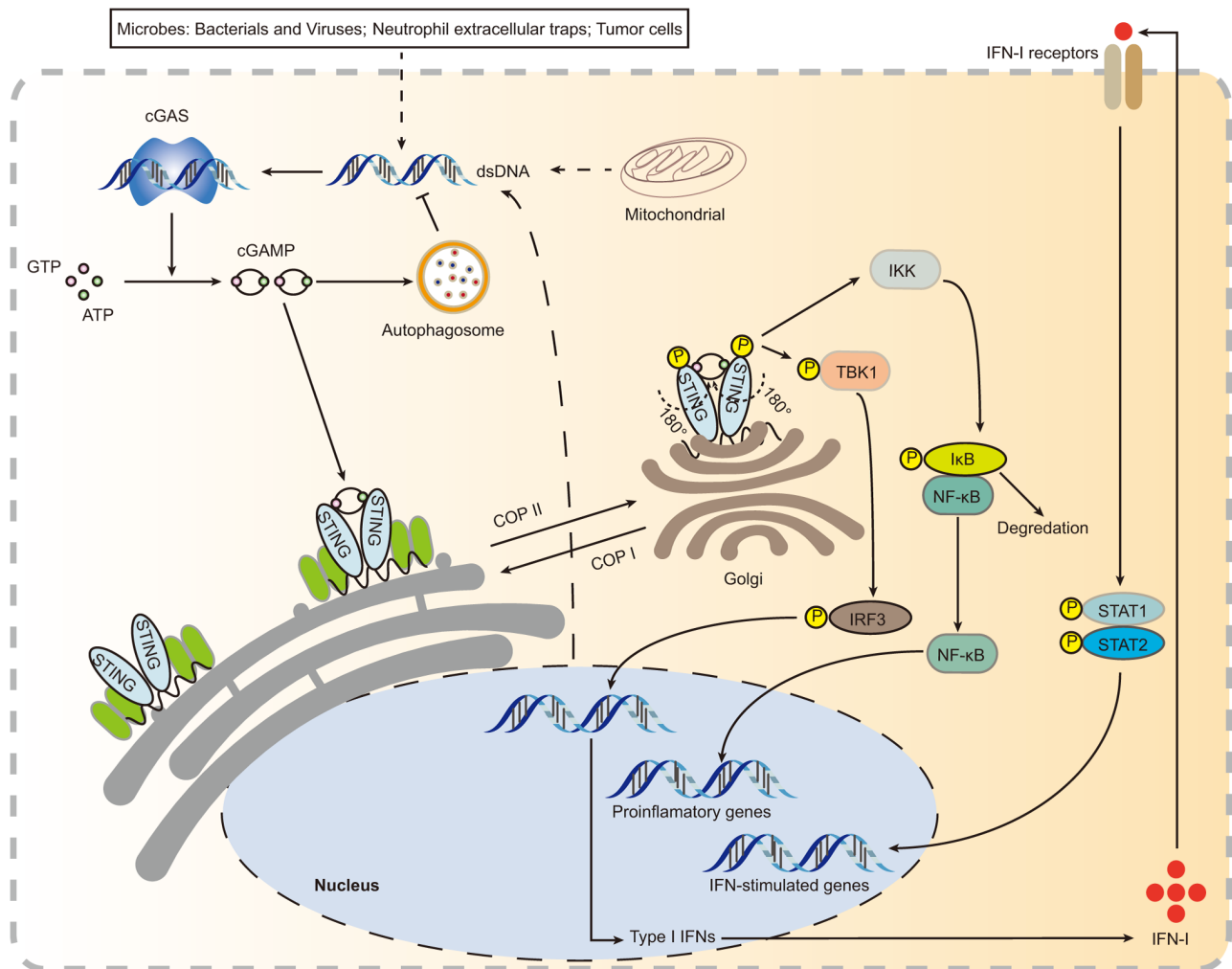


Figure 1. Overview of the cGAS-STING pathway. Based on the cytosolic DNA stimulation, cGAS promotes the production of cGAMP. Second messenger cGAMP binds to STING on the endoplasmic reticulum, then the cGAMP-STING complex is translocated to the Golgi apparatus by COP II protein. Following this translocation, STING can promote the expression of type I IFNs and proinflammatory genes through the STING-p-TBK1-IRF3 signaling and NF-κB pathways, respectively. Furthermore, secreted type I IFNs can effectively stimulate the expression of ISGs in response cells. These effector molecules, such as type I IFN, IL-6 and ISGs, exert important effects on tumor cells and immune cells. Notably, cGAMP can promote autophagy formation, which may suppress the cGAS-STING pathway by degrading cytosolic dsDNA. cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; IRF3, IFN regulatory factor 3; IKK, inhibitor of κB kinase; IκB, inhibitor of κB; IFN, interferon; ISG, IFN-stimulated gene; COP I/II, coat protein complex I/II.

of mitochondrial transcription factor A (TFAM) to inhibit the cGAS-STING pathway to fuel tumor development (35). These results reveal that there are multiple regulatory factors in OSCC cells that limit cGAS-STING expression to promote tumor progression.

Influences of the cGAS-STING pathway on the immune microenvironment. Activation of the cGAS-STING pathway mediates the secretion of IFN-β and chemokines, reshaping the immune landscapes within the TME. In OSCC, tumor cell-intrinsic cGAS-STING pathway activation promotes the infiltration and function of both CD8⁺ T cells and DCs (36), induces macrophage polarization into M1 (37) and reduces Treg infiltration (34). In HPV⁺ OSCC, STING activation also potentiates cetuximab-mediate NK cell cytotoxicity and DC maturation (38). Additionally, type I IFN can induce ferroptosis in OSCC cells through a mechanism involving the downregulation of glutathione peroxidase 4 (GPX4) by phosphorylated FOXO1 (39). Apoptotic OSCC cells dampen

the cGAS-STING pathway in cancer associated fibroblasts (CAFs), reducing type I IFN secretion, which promotes the proliferation of tumor cells (40). These reports highlight that cGAS-STING mediates the regression of OSCC by enhancing antitumor immunity and inhibiting tumor cell proliferation.

Context-dependent effects and therapeutic implications of the cGAS-STING pathway. As aforementioned, most studies indicate that cGAS-STING pathway activation in tumor cells drives antitumor immunity and may represent a promising strategy for OSCC treatment. However, Li *et al* (41) found that cGAS expression is also associated with the recurrence and metastasis of OSCC. Mechanistically, physical matrix stiffness induces DNA damage and non-canonical cGAS-STING activation within tumor cells, directly driving epithelial-mesenchymal transition (EMT) and invasiveness (41). This finding highlights the complex role of the cGAS-STING pathway in OSCC. This complexity may stem from its involvement in both regulating the malignant phenotype of tumor

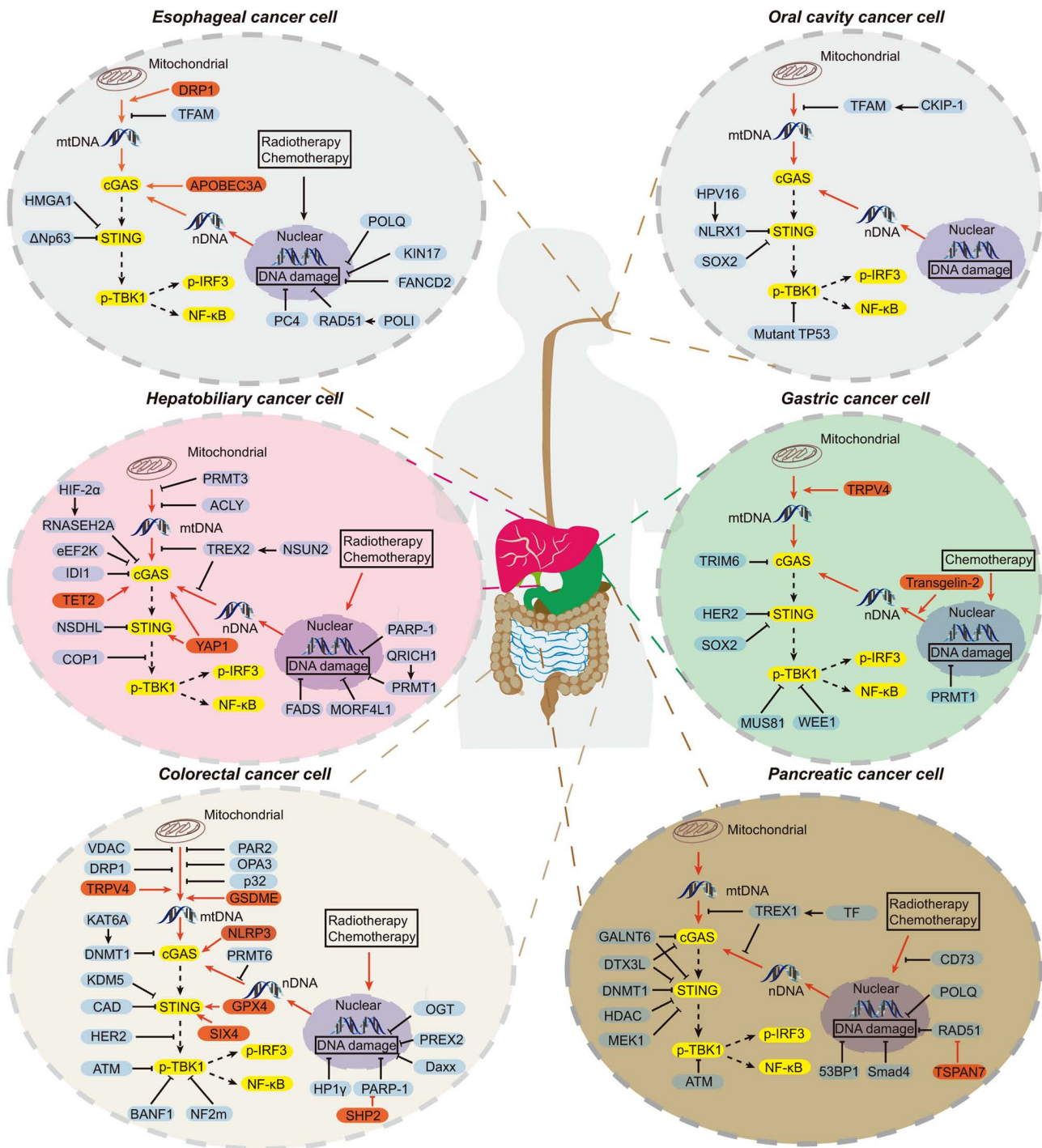


Figure 2. Regulatory mechanisms of the cGAS-STING pathway in malignant cells in digestive system cancer types. In tumor cells, abnormal cytosolic DNA accumulation is the main stimulator for the activation of this pathway, which can be triggered by traditional chemotherapy and radiotherapy. While certain molecules within tumor cells, such as the TRPV4 protein in gastric and colorectal cancer, can promote the cGAS-STING pathway, tumor cells more frequently employ intrinsic molecules to inhibit this pathway, leading to tumor progression. Arrow-headed and bar-headed lines represent activation and inhibition, respectively. cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; p, phosphorylated; TRPV4, transient receptor potential vanilloid 4.

cells and shaping the TME. The biological consequences of cGAS-STING activity in OSCC reflect the interactions between viral status, tumor cell- or immune cell-intrinsic signaling, immune composition and physical matrix stiffness. Therefore, therapeutic strategies targeting this pathway should be context-stratified to maximize antitumor efficacy while minimizing potential pro-metastasis risk. However, most studies have shown that activation of this pathway can drive

antitumor immunity and may represent a promising strategy for OSCC treatment.

Esophageal cancer

Clinical associations and heterogeneity of the cGAS-STING pathway. Esophageal squamous cell carcinoma (ESCC) accounts for the majority of esophageal cancer cases (42). Compared with the adjacent normal tissue, STING is lowly

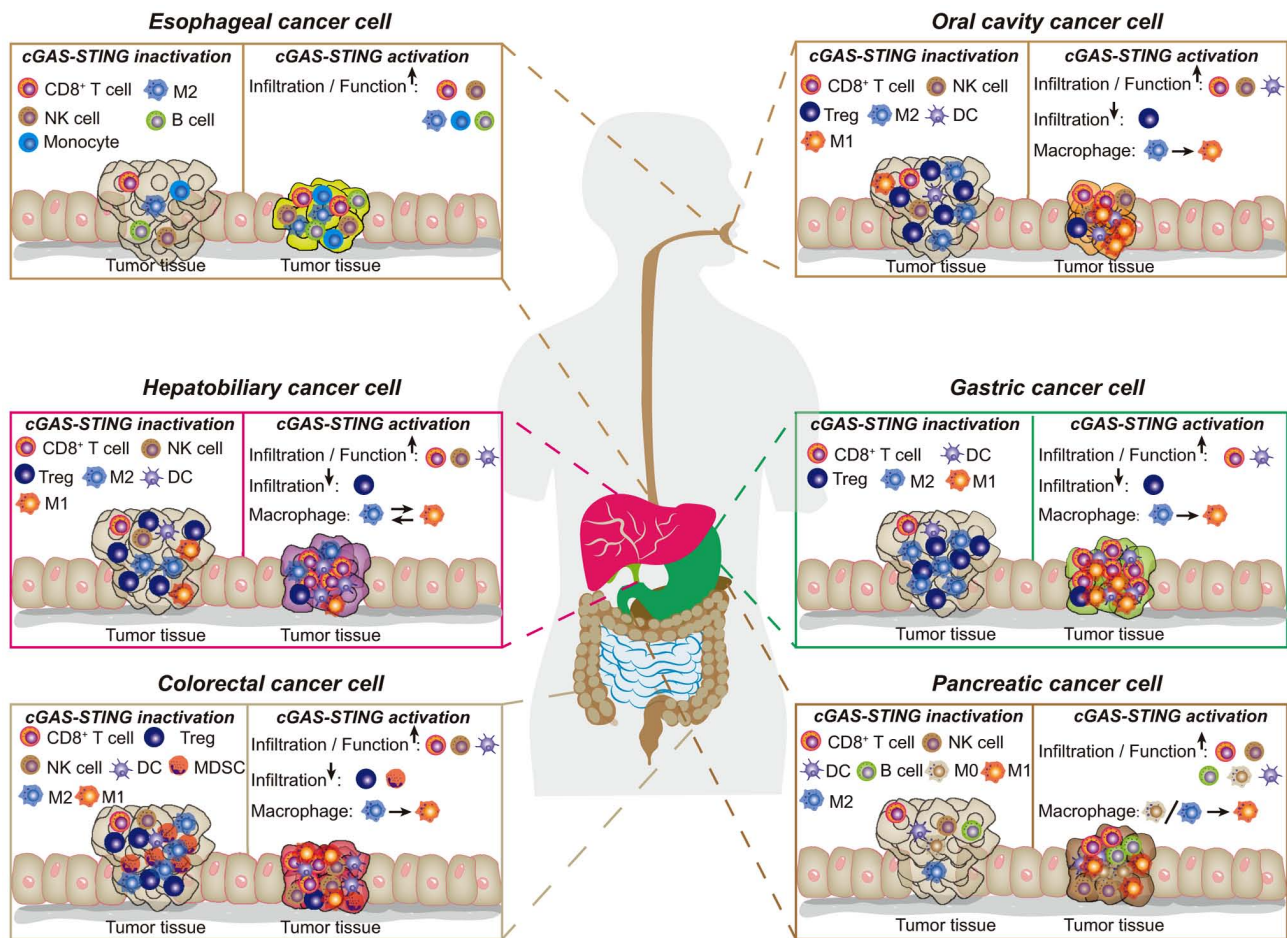


Figure 3. Influence of the cGAS-STING pathway on the immune landscape in digestive system cancer types. Activation of the cGAS-STING pathway significantly remodels the tumor immune microenvironment in digestive system cancer types. This activation consistently enhances the infiltration and functional activity of CD8⁺ T cells and DCs; it also promotes the recruitment of NK cells across a range of malignancies, including oral, esophageal, hepatobiliary, pancreatic and colorectal cancer. However, its effects on macrophages are context-dependent: cGAS-STING signaling can promote antitumor macrophage activation in some tumors, while in others it may drive immunosuppressive phenotypes, including M2 polarization in hepatocellular carcinoma and esophageal squamous cell carcinoma or BST2⁺ macrophage formation in pancreatic ductal adenocarcinoma. Therefore, the effect of cGAS-STING signaling in macrophages may be context-dependent. The comprehensive biological consequence of cGAS-STING activation in digestive system cancer types still needs to be considered from different perspectives, such as tumor molecular subtypes, disease stage and activating factors. M1, M1 macrophage; M2, M2 macrophage; Treg, regulatory T cell; DC, dendritic cell; MDSC, myeloid-derived suppressor cell; NK, natural killer; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes.

expressed in ESCC and suppresses tumor progression by inhibiting fatty acid β -oxidation (43). However, in patients with ESCC and intratumoral *Fusobacterium nucleatum* infection, STING expression is negatively associated with a favorable prognosis (44). Li *et al* (45,46) found that dynamin-related protein 1 (DRP1) overexpression or TFAM knockdown can disrupt mitochondrial function of ESCC cells, which then activates the cGAS-STING pathway to promote autophagy-mediated tumor growth. These findings may indicate the complexity of this pathway in ESCC.

Tumor cell-intrinsic regulatory mechanisms of the cGAS-STING pathway. Currently, most studies demonstrate that the tumor cell-intrinsic cGAS-STING pathway functions as a tumor suppressor in ESCC. Tumor cells utilize multiple mechanisms to restrain this pathway for ESCC progression. For instance, high mobility group A1 and tumor protein p63 isoform inhibit STING expression to promote tumor progression (47,48). As a DNA damage sensor, the cGAS-STING pathway can be inhibited by maintaining DNA stability. By

mediating DNA damage repair via interacting with DEXH-box helicase 9, DNA/RNA-binding protein KIN17 fuels ESCC progression by dampening STING activation (49).

Conversely, promoting DNA damage may effectively trigger this pathway in ESCC. Knockout of DNA polymerase θ (POLQ) and/or fanconi anemia group D2 protein markedly increases genomic instability in ESCC cells, which elevates cGAS expression and activates the cGAS-STING pathway, ultimately promoting tumor regression (50). Moreover, following DNA damage, apolipoprotein B mRNA editing enzyme catalytic polypeptide 3A induces cGAS-STING signaling activation and increases immunotherapy efficacy by promoting cytosolic DNA accumulation in ESCC (51). Collectively, upregulation of cGAS-STING expression or induction of DNA damage can activate the tumor cell-intrinsic cGAS-STING pathway, resulting in ESCC regression.

Therapy-induced activation and TME remodeling. As the common therapeutic strategies for ESCC, radiotherapy

and chemotherapy are powerful inducers of DNA damage. Studies have demonstrated that radiotherapy with different doses [24 Gy/3 fractions (F) or 30 Gy/10 F] can effectively trigger the cGAS-STING pathway in tumor cells by inducing DNA damage (52,53). Meanwhile, promoting DNA damage repair acts to inhibit radiotherapy-induced activation of this pathway. DNA polymerase ϵ stabilizes DNA repair protein RAD51 by suppressing the activity of E3 ubiquitin-protein ligase XIAP, which in turn inhibits the cGAS-STING pathway and promotes radiotherapy resistance (54). Thus, the radio-sensitivity of ESCC is tightly associated with cGAS-STING pathway activity (55). Besides radiotherapy, chemotherapy drugs, such as 5-fluorouracil (5-FU) and cisplatin, have also been found to activate this pathway by DNA damage (56). These reports demonstrate the positive effect of chemoradiotherapy on cGAS-STING pathway activation.

Tumor cell-intrinsic cGAS-STING pathway activation also affects the immune landscape in ESCC. Pathway activation induced by radiotherapy can increase the infiltration of CD8⁺ T cells and CD163⁺ M2 macrophages (52) as well as promote the recruitment of circulating monocytes into the tumor microenvironment to enhance antitumor immunity (53). Positive cofactor 4, promoter of DNA repair, can inhibit the cGAS-STING pathway triggered by radiotherapy, reducing the numbers of CD8⁺ tumor-infiltrating lymphocytes (TILs) and GZMB⁺ CD8⁺ TILs in ESCC (57). Additionally, chemotherapy-mediated activation of the cGAS-STING pathway can promote the secretion of interferon β 1 (IFNB1), C-X-C motif ligand 10 (CXCL10) and chemokine (C-C motif) ligand 5 (CCL5) from ESCC cells and facilitate the infiltration of CD8⁺ T cells and CD163⁺ M2 macrophages (56). Overall, traditional therapeutic strategies, such as radiotherapy and chemotherapy, can stimulate cGAS-STING signaling in malignant cells to reshape the TME of ESCC.

Therapeutic implications and subtype-specific caveats of the cGAS-STING pathway. Triggering the cGAS-STING pathway in tumor cells increases the infiltration of monocytes and CD8⁺ T cells, which enhances the immune-mediated tumor control. Paradoxically, the same activation also enhances the infiltration of CD163⁺ M2 macrophage to counteract anti-cancer immunity (52,56). Hence, the net effect of the tumor cell-intrinsic cGAS-STING pathway on ESCC progression is variable and largely dictated by the immunological composition of the TME. Therefore, inhibiting immunosuppressive cells may enhance the therapeutic efficacy of activating this pathway in ESCC treatment. Notably, regarding the role of the cGAS-STING pathway in esophageal cancer, current evidence primarily focuses on OSCC. Whether these conclusions can be generalized to esophageal adenocarcinoma remains uncertain and is an important direction for future research.

GC

Clinical associations and subtype-associated heterogeneity of the cGAS-STING pathway. cGAS protein is highly expressed in GC tissues compared with normal adjacent tissues (58), and a prognostic model based on the cGAS-STING pathway-related genes has been developed in GC (59). However, the cGAS-STING pathway exhibits notable heterogeneity in GC, likely related to different molecular subtypes. In human epidermal growth factor receptor 2 positive (HER2⁺) GC,

HER2 can mediate low STING expression via AKT signaling, which is associated with low infiltration of CD8⁺ T cells (60). Moreover, HER2 upregulation promotes the migration of GC cells by suppressing the cGAS-STING pathway (61). These findings suggest that the functional status of the cGAS-STING pathway may differ across clinically relevant molecular subtypes of GC. Notably, dMMR tumors often exhibit a stronger cGAS-STING activity, while HER2 tends to inhibit this pathway in GC and limit antitumor immune responses.

Tumor cell-intrinsic regulatory mechanisms of the cGAS-STING pathway. Beyond these subtype-associated differences, accumulating evidence indicates that the tumor cell-intrinsic cGAS-STING pathway generally functions against GC and tumor cells develop multiple mechanisms to modulate this pathway. In addition to HER2, tripartite motif containing (TRIM) 6 directly inhibits STING expression and mediates cGAS degradation (60,62). SOX2 also deactivates this pathway by promoting AKT phosphorylation to promote GC development (63).

Furthermore, cytoplasmic accumulation of dsDNA can also activate this pathway. In GC, the cGAS-STING pathway is triggered by transient receptor potential vanilloid 4-induced cytoplasmic Ca²⁺-related oxidized mtDNA (64), protein arginine N-methyltransferase 1 knockdown-mediated dsDNA accumulation (65) and transgelin-2-related cytosolic ssDNA accumulation (66). Moreover, oxaliplatin can activate this pathway to combat GC through inducing DNA damage (67). These reports demonstrate that GC cells employ multiple endogenous molecules to govern cGAS-STING signaling. Cytosolic DNA accumulation represents an important inducer for this signaling activation.

TME remodeling. Tumor cell-intrinsic cGAS-STING pathway activation can reshape the TME of GC by inducing the secretion of multiple inflammatory cytokines and chemokines. As aforementioned, HER2 expression results in decreased CD8⁺ T cell infiltration in GC by inhibiting this pathway and reducing the secretion of type I IFNs and T cell chemokines (60). Conversely, weel-like protein kinase inhibition combined with methyl methanesulfonate and ultraviolet-sensitive gene 81 knockdown promotes the accumulation of cytosolic double-stranded DNA to activate the cGAS-STING pathway, leading to TBK1 phosphorylation and the secretion of proinflammatory cytokines (CCL20, CXCL10 and IFNB1) from MFC cells, which then effectively enhance CD8⁺ T cell infiltration and anti-programmed death ligand 1 (PD-L1) efficacy (68). Additionally, cGAS-STING pathway activation in tumor cells can promote DC maturation, M1 macrophage polarization (64) and enhance the function of DCs and CD8⁺ T cells to promote antitumor immune responses (69). Collectively, these reports reveal that activation of the cGAS-STING pathway in tumor cells promotes the antitumor immunity in GC by TME remodeling.

However, the contribution of cGAS-STING signaling in GC is not restricted to tumor cells. In a study of 154 newly diagnosed GC cases, STING expression in non-tumor cells was also positively correlated with the infiltration of antitumor immune cells (70). Therefore, the therapeutic potential of cGAS-STING activation may extend beyond tumor cells to encompass immune cells. In macrophages, Dickkopf-1 knockdown facilitates the M1 polarization of macrophages

and then enhances the antitumor immune response in GC (71). Engineered low-pathogenic *Helicobacter pylori* can also initiate the cGAS-STING pathway to repolarize macrophages into an antitumor M1 phenotype (72). These observations further indicate that this pathway in tumor and immune cells may cooperatively induce an immune-active TME in GC.

Therapeutic implications and challenges of the cGAS-STING pathway. The relationship between cGAS-STING activation and antitumor immunity is not entirely linear. A critical caveat is that activation of this pathway also upregulates PD-L1 expression in GC cells (66), suggesting that cGAS-STING-driven immune activation may simultaneously induce compensatory immune checkpoint response. Therefore, synergistic combination of activating this pathway with PD-1 or PD-L1 blockade holds promise for suppressing the immune evasion of GC. Taken together, these findings suggest that the value of activating cGAS-STING in GC treatment may depend on molecular subtypes, cellular compartments and accompanying innate and adaptive immune responses.

Hepatobiliary cancer

Clinical associations and heterogeneity of the cGAS-STING pathway in hepatocellular carcinoma (HCC). In HCC, the cGAS-STING pathway exhibits dual or paradoxical roles. The biological consequence of this pathway may depend on tumor type, cellular compartment, disease stage and the context in which the pathway is activated. For example, cGAS and STING can exert tumor-suppressive effects in established HCC, as cGAS inhibits AKT-mTORC1 signaling and STING deficiency is associated with increased tumor burden at late stages (73,74), whereas STING signaling can exacerbate immune-mediated damage and facilitate tumor initiation in the chronic liver disease model (Mcl1^{Δhep} mice), illustrating a pro-tumorigenic role in specific settings (75). In addition, macrophage-intrinsic STING signaling can either promote chronic inflammation and carcinogenesis or enhance antitumor T-cell responses (11,76). Moreover, the context of pathway activation is important. For instance, radiotherapy-induced cGAS-STING pathway activation can promote antitumor immune remodeling (77), while also contributing to compensatory PD-L1 upregulation in tumor cells (78). Taken together, these reports suggest that the effect of STING signaling in HCC may differ between established tumors and chronic inflammatory conditions preceding tumor development, emphasizing the importance of disease stage and inflammatory context.

Tumor cell-intrinsic regulatory mechanisms of the cGAS-STING pathway in HCC. HCC cells have evolved diverse mechanisms to suppress the cGAS-STING pathway. One major strategy by which tumor cells restrict this pathway is to prevent the accumulation of cytosolic DNA. NOP2/Sun RNA methyltransferase family member 2 can stabilize the expression of three prime repair exonuclease 2, which then inactivates this pathway by degrading cytosolic DNA to induce both tumorigenesis and anti-PD-L1 therapy resistance in HCC (79). Hypoxia-induced hypoxia-inducible factor 2α expression upregulates ribonuclease H2 subunit A to dampen DNA-mediated activation of the cGAS-STING pathway in HCC (80). Following anti-PD1 therapy, effector T cell-derived IFN-γ can upregulate the expression of

arginine methyltransferase (PRMT) 3 in tumor cells, which mediates HSP60 arginine methylation to inhibit mitochondrial DNA leakage and then inactivate the cGAS-STING pathway (81). Other molecules, including flavin adenine dinucleotide synthase, adenosine 5'-triphosphate citrate lyase, glutamine-rich protein 1 and mortality factor 4-like 1 (MORF4L1) also attenuate activation of this pathway by reducing reactive oxygen species-induced DNA damage, mitochondrial damage or promoting DNA damage repair (82-85). Collectively, these findings demonstrate that HCC cells employ multiple endogenous molecules to suppress tumor cell-intrinsic STING signaling by preventing cytosolic DNA accumulation.

Another mechanism is to regulate the expression of cGAS and STING. Isopentenyl-diphosphate delta-isomerase 1 recruits the E3 ligase TRIM41 to promote cGAS ubiquitination and degradation, thereby inhibiting the cGAS-STING pathway and promoting HCC progression (86). Methylcytosine dioxygenase teneleven translocation-2, which is lowly expressed in HCC, can upregulate cGAS expression in tumor cells by promoting cGAS demethylation (13). Additionally, knockout of eukaryotic elongation factor 2 kinase (eEF2K) has been shown to restore the activity of this pathway by upregulating the expression of cGAS and STING in HCC cells (87). Together with the mechanisms that limit cytosolic DNA accumulation, these findings indicate that HCC cells suppress cGAS-STING signaling at multiple levels, ranging from the generation of stimulatory DNA to the expression of core pathway components.

TME remodeling after tumor cell-intrinsic pathway activation in HCC. Genotoxic therapies, such as chemotherapy or radiotherapy, activate the tumor cell-intrinsic cGAS-STING pathway, leading to the secretion of proinflammatory cytokines and TME remodeling (77,88,89). Following activation of this pathway, changes in the immune landscape of the TME involve DC activation, increased infiltration of neutrophil, CD4⁺ T and CD8⁺ T cells, enhanced NK cell activity and reduced Treg infiltration (77,79,90-92). Notably, while cisplatin can upregulate the expression of cGAS and STING by enhancing Yes-associated protein 1 expression in HCC, cGAS-STING pathway activation also induces hepatotoxicity (93,94). Furthermore, abnormal activation of this pathway also increases PD-L1 expression in tumor cells, which may restrict the function of CD8⁺ T cells (78,95). Therefore, although tumor cell-intrinsic cGAS-STING pathway activation generally promotes antitumor immunity in HCC, available evidence also indicates that, under certain conditions, this pathway may be associated with hepatotoxicity and increased PD-L1 expression. These findings further indicate that the biological outcomes of pathway activation depend not only on whether cGAS-STING is activated, but also on the pathological context of its activation.

Immune cell- and stromal cell-intrinsic cGAS-STING pathways in HCC. Beyond tumor cells, cGAS-STING signaling in immune and stromal cells also critically influences HCC progression. In macrophages, this pathway can exert opposing effects. Tumor cell-derived extracellular vesicles containing mtDNA, can facilitate M2 polarization to dampen antitumor immunity (96). Similarly, following uptake of dsDNA, macrophage-intrinsic cGAS-STING activation can

induce liver chronic inflammation, mediating liver damage and carcinogenesis (11). Conversely, macrophage-intrinsic cGAS-STING activation can promote the infiltration of CD8⁺ T cells to kill senescent cancer cells (97) and enhance type I IFN-triggered antitumor immunity in HCC (76). Thus, macrophage-intrinsic cGAS-STING activation leads to either protumor or antitumor outcomes in HCC. A possible explanation for these opposing outcomes is that the effects of macrophage-intrinsic cGAS-STING signaling on HCC may depend on the type of stimuli, the state of macrophages and the cross-talk with other cells in the TME. Therefore, its role in HCC is highly context-dependent.

In contrast to the context-dependent effects observed in macrophages, cGAS-STING activation in DCs more consistently supports antitumor immunity in HCC (98,99). Tumor cell-derived signals, including exosome-related circular RNA TMEM56 and DNA released from HCC cells after sorafenib treatment, can potentiate endogenous STING signaling in DCs to mediate type I IFN secretion and increase the antitumor effects of CD8⁺ T and NK cells (100,101). This response can also be enhanced by targeting CD47, which facilitates the uptake of tumor-associated DNA by CD103⁺ DCs to activate the cGAS-STING pathway and then induces the secretion of IL-12 and CXCL9 from DCs to recruit NK cells into HCC (102). Furthermore, cGAS-STING activity in DCs is positively associated with radiotherapy sensitivity in HCC (103,104). Notably, tumor-derived cGAMP can trigger STING signaling in endothelial cells to normalize abnormal tumor vasculature, which facilitates CD8⁺ T cell infiltration into HCC (13). Taken together, existing evidence more consistently supports an antitumor role of DC- and endothelial cell-intrinsic cGAS-STING signaling in HCC.

Therapeutic strategies targeting the cGAS-STING pathway in HCC. Multiple strategies have been demonstrated to activate the cGAS-STING pathway in tumor cells. Firstly, traditional chemotherapy and radiotherapy can induce DNA damage to mediate the activation of this pathway in HCC (92,105). Olaparib, a poly (ADP-ribose) polymerase 1 inhibitor, can enhance radiotherapy-mediated cGAS-STING activation by inhibiting DNA damage repair in HCC (106). In turn, activation of this pathway in tumor cells can amplify the efficacy of radiotherapy in HCC (107). Both Mn²⁺ and hyperbaric oxygen treatment also potentiate chemotherapy-induced activation of the cGAS-STING pathway in HCC (88). Additionally, targeting upstream negative regulators, such as genetic depletion of PRMT3, MORF4L1 or eEF2K, represents another effective strategy to relieve the intrinsic inhibition of the cGAS-STING pathway by tumor cells and restore or enhance tumor sensitivity to radiotherapy, chemotherapy and immunotherapy (81,85,87). Precise delivery of cGAS-STING activators is another important direction. For instance, delivering STING agonist specifically to DCs can trigger this pathway to enhance antitumor immunity (98). Given the context-dependent effects of this pathway, therapeutic activation may be most beneficial when it targets favorable compartments, particularly tumor cells and DCs, for minimizing hepatotoxicity, chronic inflammation or immunosuppressive macrophage response.

cGAS-STING signaling in intrahepatic cholangiocarcinoma (ICC). Compared with HCC, available evidence

regarding the effect of cGAS-STING signaling in ICC remains limited. In ICC, the type I IFN induced by this pathway can fuel tumor growth by activating Janus kinase 2 (JAK2)/STAT5 signaling (108). However, cGAS-STING activation can also be associated with enhanced antitumor immunity in specific molecular contexts. Compared with Epstein-Barr virus (EBV)⁻ patients, EBV⁺ patients are more likely to benefit from anti-PD1 therapy (109). Mechanistic analysis reveals that EBV⁺ ICC cells exhibit enhanced cGAS-STING pathway activity, which promotes the secretion of IFN α , IFN β 1, interferon-stimulated gene 15, IL6 and CXCL10 as well as increases CD8⁺ T cell infiltration (109). Coat protein complex I inhibition suppresses the progression of ICC by activating the cGAS-STING pathway (110). Moreover, 3-hydroxysteroid dehydrogenase can facilitate the degradation of STING to inhibit the cGAS-STING pathway, resulting in the reduced infiltration of NK cells, activated CD4⁺ T cells and neutrophils (111). However, tumor-derived mtDNA activates this pathway to polarize macrophages toward an M1 phenotype, thereby enhancing the antitumor immune response (112). These observations indicate ICC cells employ diverse mechanisms against the cGAS-STING pathway, and the biological consequence of cGAS-STING signaling in ICC may depend on both the cellular compartment and tumor-associated characteristics such as EBV status.

cGAS-STING signaling in gallbladder cancer. Evidence discussing the role of the cGAS-STING signaling pathway in gallbladder cancer is more limited. Activation of the cGAS-STING pathway in gallbladder cancer cells can enhance NK cell-mediated antitumor immune response (113). Although this observation supports the role of this pathway in suppressing gallbladder cancer, the evidence is limited and needs further exploration in future studies.

Summary of the role of cGAS-STING signaling in hepatobiliary cancer. Taken together, cGAS-STING signaling plays complex and context-dependent roles in hepatobiliary cancer. In HCC, its effects are shaped by disease stage, inflammatory context, tumor-intrinsic suppressive mechanisms and immune or stromal cell compartments. While several reports suggest that the tumor cell-intrinsic cGAS-STING pathway promotes tumor progression, most studies demonstrate that activation of this pathway can boost antitumor immunity and mediate tumor regression in HCC. In ICC, the effects of cGAS-STING signaling appear to depend on both the molecular context, such as EBV status, and the cellular compartment. Although pathway activation may promote tumor growth through type I IFN-JAK2-STAT5 signaling in some settings, it can enhance antitumor immunity in EBV⁺ tumors and in macrophages by increasing CD8⁺ T-cell infiltration or promoting M1 polarization. In gallbladder cancer, limited evidence suggests that tumor cell-intrinsic cGAS-STING activation can enhance NK cell-mediated antitumor responses; however, its underlying mechanisms and potential effects in other immune or stromal compartments remain largely unclear.

In summary, these reports suggest that cGAS and STING play complex roles in the development of hepatobiliary cancer. The conflicting functions of this pathway are likely due to biological differences among tumors, rather than simply contradictory experimental results.

Pancreatic cancer

Clinical associations and heterogeneity of the cGAS-STING pathway. Only half of pancreatic ductal adenocarcinoma (PDAC) tissues collected from patients express cGAS protein (114). Elevated expression of cGAS and STING in patients with PDAC is associated with improved clinical outcomes (115), indicating that the cGAS-STING pathway may function against PDAC. Indeed, the activation of this pathway in tumor cells promotes the expression of IFN- β , CCL5 and CXCL10, which subsequently facilitates the infiltration of effector immune cells and inhibits PDAC immune escape (116). However, some studies also indicate that activation of this pathway in PDAC cells contributes to tumor progression by inducing dual oxidase 2 expression (117) and chemotherapy resistance (118) as well as increasing tumor stemness and metastasis (119,120). These contradictory findings indicate that the effect of cGAS-STING pathway activation in PDAC is context-dependent rather than simply an antitumor or protumor effect. However, most current studies support that activation of the tumor cell-intrinsic cGAS-STING pathway has a tumor suppressive role through the production of inflammatory mediators and TME remodeling.

Tumor cell-intrinsic regulatory mechanisms of the cGAS-STING pathway. In PDAC cells, the cGAS-STING pathway is mainly activated by cytoplasmic DNA accumulation resulting from genomic instability or impaired DNA damage repair. Several mechanisms can promote this process. For instance, tetraspanin 7 promotes DNA damage by downregulating the expression of RAD51-associated protein 1, thereby inhibiting RAD51-associated protein 1-mediated DNA repair and then activates the cGAS-STING pathway to foster antitumor immunity (121). Depletion of TP53-binding protein 1 or inhibition of POLQ can activate the cGAS-STING pathway by increasing micronuclei or double-stranded DNA (122,123). Similarly, inhibition of tissue factor promotes the proteasome degradation of three-prime repair exonuclease 1 (TREX1), leading to intracellular micronuclei accumulation and cGAS-STING pathway activation (124). Traditional chemotherapy and radiotherapy also trigger the activation of this pathway in tumor cells by inducing DNA damage (118,125). Thus, the amount and persistence of cytosolic DNA appear to be important factors for cGAS-STING pathway activation in PDAC cells.

PDAC cells employ multiple strategies to suppress cGAS-STING pathway activation. For example, CD73 and Smad4 attenuate chemoradiotherapy-induced DNA damage and the spontaneous DNA damage of tumor cells, respectively, resulting in limited cGAS-STING signaling in PDAC (126,127). Additionally, polypeptide *N*-acetylgalactosaminyltransferase 6 and the E3 ligase DTX3L promote the degradation of STING and cGAS, respectively (114,116), while DNA (cytosine-5)-methyltransferase 1 (DNMT1) and histone deacetylase can suppress STING expression by epigenetic mechanisms (128,129). Furthermore, other signals also influence the activity of the cGAS-STING pathway. MEK inhibition alone or combined with autophagy blockade can effectively activate the STING signaling and enhance STING-dependent type I IFN production (130,131). Inhibiting ataxia-telangiectasia mutated (ATM) activates TBK1 by SRC phosphorylation in a cGAS-independent pathway (132). Moreover, by inhibiting AKT phosphorylation, metformin

activates the cGAS-STING pathway to facilitate T cell infiltration into PDAC (133). Thus, tumor cell-intrinsic cGAS-STING signaling is controlled by the balance between cytosolic DNA accumulation and other suppressive signals in PDAC.

Immune cell- and stromal cell-intrinsic cGAS-STING pathways. Beyond tumor cells, the cGAS-STING pathway in immune and stromal cells also influences the progression of PDAC. On the one hand, STING signaling in macrophages has been associated with pancreatic tumorigenesis and CD8⁺ T cell exhaustion (134,135). On the other hand, PKR-like ER kinase deletion in myeloid cells (via *Lyz2*^{Cre}) or annexin A1 inhibition in macrophages enhances the STING-dependent type I IFN response and promotes antitumor immunity in PDAC models (136-138). These reports reveal that macrophage-intrinsic STING signaling can induce either immunosuppressive or antitumor effects, depending on the activation state and surrounding microenvironment.

In B cells, STING activation can promote IL35 expression in an IRF3-dependent manner, while IL35⁺ regulatory B cells subsequently suppress NK cell function (12). In addition, activation of this pathway in PDAC has been found to be associated with the characteristics of CAFs (115). These studies indicate that this pathway functions differently across various immune cells and stromal cells in PDAC. Therefore, the effects of cGAS-STING signaling in PDAC should be considered from multiple levels.

Therapeutic implications and challenges of the cGAS-STING pathway. Currently, increasing evidence indicates that tumor cell-intrinsic cGAS-STING pathway activation boosts the immune response against PDAC. Chemokines (CXCL9, CXCL10 and CCL5) and type I IFN, generated by activation of this pathway, can effectively recruit and activate CD8⁺ T cells, NK cells and DCs (122,124,139), while promoting the formation of M1 macrophage (137,138). Consistent with this immunostimulatory function, the STING agonist D166 remodels the tumor immune microenvironment and improves the antitumor immune response in PDAC (140). This signaling activation also enhances the efficacy of various treatments, including chemotherapy (139,141), radiotherapy (125), immunotherapies [ICIs (142) and CAR-NK therapy (143)] and irreversible electroporation therapy (144). In apoptosis-resistance PDAC cells, smac mimetic BV6 can synergize with STING to induce the necroptosis of tumor cells (145).

Taken together, tumor cell-intrinsic cGAS-STING pathway activation frequently enhances inflammatory chemokine production and immune-cell recruitment, whereas particular signaling contexts may promote chemotherapy resistance, tumor stemness or metastasis. Macrophage intrinsic STING signaling can support either immunosuppressive or antitumor responses and activation of this signaling pathway in IL35⁺ regulatory B cells functions against NK cell function. Thus, activating the cGAS-STING pathway in PDAC treatment should maximize antitumor immunity while minimizing potentially tumor-promoting effects in specific immune or malignant-cell states.

CRC

Clinical associations and heterogeneity of the cGAS-STING pathway. Compared with adjacent normal tissues, the

expression of cGAS, phosphorylated (p-)STING, p-TBK1 and p-IRF3 is significantly reduced in CRC (146). Furthermore, low expression of cGAS and STING is tightly associated with radiotherapy resistance, metastasis and immune escape in CRC (147-149). However, the activity of the cGAS-STING pathway may vary substantially across different molecular subtypes. Based on microsatellite instability (MSI) status, MSI-type CRC comprises two subtypes: dMMR/MSI high(-H) and pMMR/MSI low(-L) (150). In a study, among 243 patients with CRC and pMMR/MSI-L, 76.1% of patients lacked the cGAS protein and 70.8% did not express the STING protein; patients expressing both proteins had a higher 5-year recurrence-free survival rate, indicating cGAS/STING expression benefits pMMR patient survival (151). By contrast, dMMR cases show upregulated cGAS/STING expression associated with enhanced CD8⁺ T cell infiltration (9,152). Compared with pMMR CRC, dMMR CRC exhibits higher tumor mutational burden, with an improved therapeutic response of ICIs (153,154). Therefore, the differential expression of cGAS and STING between pMMR and dMMR CRC may partially account for their distinct responses to ICI therapy.

Tumor cell-intrinsic regulatory mechanisms of the cGAS-STING pathway. Most experimental evidence supports a tumor-suppressive role of the tumor cell-intrinsic cGAS-STING pathway in CRC. Genetic deletion of cGAS or STING accelerates inflammation-associated tumorigenesis and CRC progression (155,156), indicating that this pathway may inhibit the development of early CRC. When combined with STING agonists, oxaliplatin liposomes significantly activate the STING signaling in tumor cells, which then facilitates the infiltration of CD8⁺ T cells and M1 polarization and restricts Tregs recruitment (157). Similarly, cytotoxic 5-FU also activates tumor cell-intrinsic cGAS-STING signaling to drive IFN- β production, which then induces M1 polarization (158). In CT26 and MC38 preclinical models, activating this pathway in tumor cells could improve the cytotoxicity of CD8⁺ T and NK cells (5,159). In addition, the increased infiltration of cytotoxic CD8⁺ T cells and DCs, induced by administering STING agonists, also prevents postoperative CRC recurrence (160). These findings demonstrate that the cGAS-STING pathway in tumor cells serves as a tumor suppressor in CRC. Collectively, these findings indicate that activation of cGAS-STING signaling in CRC cells enhances tumor immunogenicity and supports antitumor immunity.

Consistent with this tumor suppressive function, CRC cells have developed multiple mechanisms to attenuate the activity of this pathway. A primary strategy, by which tumor cells inhibit cGAS-STING signaling, is directly disrupting this signaling cascade in CRC. Lysine acetyltransferase 6A (KAT6A) can directly inhibit cGAS expression by upregulating DNMT1 (161). DNA fragmentation factor subunit β impairs STING dimerization and inhibits STING binding to cGAMP, thereby suppressing radiotherapy-induced STING signaling (162). Furthermore, HER2 interferes with STING-TBK1 binding by promoting AKT1-mediated TBK1 phosphorylation to suppress this signaling (163,164). By down-regulating p-TBK1 and p-IRF3, barrier-to-autointegration factor 1 antagonizes this signaling to fuel MC38 progression (165). In addition, mutant NF2 protein can inhibit TBK1 activation by forming condensates with IRF3 and TBK1 (166).

Collectively, these studies show that CRC cells utilize multiple mechanisms to impair the STING signaling cascade.

Another major strategy is to prevent aberrant cytosolic DNA accumulation, by which CRC cells restrict cGAS-STING pathway. The epigenetic regulator heterochromatin protein 1 γ inhibits nuclear DNA leakage into the cytoplasm, resulting in cGAS-STING pathway inactivation in murine colon adenocarcinoma TC7 cells (167). Similarly, protease-activated receptor 2 prevents mtDNA translocation into the cytoplasm by maintaining mitochondrial membrane stability, thereby suppressing this pathway and counteracting anticancer immunity (168). *O*-linked β -N-acetylglucosamine (GlcNAc) transferase-mediated protein *O*-GlcNAcylation can inactivate the cGAS-STING pathway in tumor cells by maintaining genomic stability, which then restricts CD8⁺ T cell recruitment to fuel CRC (169). Furthermore, TREX1 can inhibit tumor cell-intrinsic STING signaling to suppress CRC progression by degrading cytosolic DNA and alleviating mtDNA stress (170). Meanwhile, PRMT6 restricts this pathway in tumor cells by reducing cytosolic DNA accumulation in CRC, resulting in resistance to ICI therapy (171). By restricting mtDNA leakage, optic atrophy 3, voltage-dependent anion channel, DRP1 and mitochondrial p32 have been found to inhibit the cGAS-STING pathway in tumor cells, leading to the progression and radiotherapy resistance of CRC (172-175). Additionally, by facilitating DNA damage repair, phosphatidylinositol-3,4,5-triphosphatedependent Rac exchange factor 2 and death domain-associated protein can effectively suppress this pathway to contribute to the chemoradiotherapy resistance of CRC (176,177). Therefore, CRC cells can also attenuate the cGAS-STING pathway by decreasing the cytosolic DNA accumulation. Beyond the aforementioned inhibitory mechanisms, ATM expression also suppresses tumor cell-intrinsic STING signaling to mediate radiation resistance in CT26 and HCT116 models (178). Similarly, lysine-specific demethylase 5 has been demonstrated to dampen this pathway to fuel CRC progression (5). Collectively, these findings suggest that targeting such suppressors (such as HER2, KAT6A and TREX1) may reactivate cGAS-STING signaling to counteract CRC progression.

Recent studies have also identified several endogenous proteins that can potentiate the cGAS-STING pathway in tumor cells. By enhancing cytosolic mtDNA translocation, gasdermin-E upregulation triggers this pathway activation in CRC cells, which drives IFN β -dependent kinase cascade and potentiates the efficacy of ICIs (179). Additionally, GPX4 sustains redox homeostasis by suppressing lipid peroxidation, amplifying cGAS-STING to drive type I IFN production and antitumor immunity in CRC (180). By promoting STING expression in CRC, sine oculis homeobox 4 can amplify STING-TBK1-IFN β signaling to exert antitumor effects (181). Similarly, NACHT, LRR and PYD domains-containing protein 3 activation also promote the cGAS-STING pathway to improve antitumor immunity in CRC cells (182). Collectively, these findings indicate that tumor cell-intrinsic cGAS-STING activity in CRC is governed by a dynamic balance between DNA damage generation, cytosolic DNA clearance, direct pathway inhibition and endogenous pathway activation.

Immune cell- and stromal cell-intrinsic cGAS-STING pathways. The cGAS-STING pathway within immune and

stromal cells also critically influences CRC progression. In T cells, low-dose STING agonist can sustain the durable tumor-eliminating capacity of CD8⁺ T cells in a CT26 tumor model (183). By contrast, tumor cell-derived cGAMP has also been shown to mediate T-cell death; STING-deficient T cells more effectively suppress tumor growth in Rag1-knockout mice bearing B16F10 or MC38 cells compared with wild-type T cells (184). These apparently opposing observations suggest that the effect of this pathway on T cells may depend on the cause and duration of STING activation, such as whether STING is activated pharmacologically or by tumor-derived cGAMP.

A similarly context-dependent result is observed in myeloid cells. Knockout of myeloid STING can inhibit macrophage maturation and DC activation (185), indicating that STING signaling may play an immunomodulatory role in myeloid cells. STING activation in macrophages induces a pro-inflammatory M1 phenotype (186), enhances NK cell function (187) and improves the antitumor immunity in a MC38 mouse model (188). However, activation of this pathway in macrophages can also induce the secretion of IL-6, which may promote the EMT process of CRC to fuel tumor progression (189). Therefore, the effect of macrophage-mediated STING signaling on CRC may depend on downstream inflammatory processes and the surrounding TME.

In DCs, CT26 cell-derived microparticles transfer DNA to DCs, which triggers the cGAS-STING pathway to induce type I IFN secretion and subsequent DC maturation (99). Similarly, the cGAS-STING pathway in DCs can be activated by the complex of oxidized low-density lipoprotein, high mobility group box-1 and genomic DNA released from CRC cells (190,191). Furthermore, STING agonists such as Mn²⁺ also facilitate the maturation of DCs in a MC38 mouse model (192). Stromal cells provide an additional level of complexity. Although CAFs can downregulate the expression of cGAS and STING in CRC cells (193), STING activation in CAFs promotes CCL4 and CCL5 expression to enhance neoadjuvant radiotherapy response in CRC by facilitating the infiltration of DCs and CD8⁺ T cells (194). Collectively, these reports highlight the complex and heterogeneous effects of the STING signaling across different immune and stromal cells in CRC.

Therapeutic implications and challenges of the cGAS-STING pathway. Inducing DNA damage and cytosolic DNA accumulation can directly activate the cGAS-STING pathway in CRC (195). Following treatment with CPT-11, 5-FU and oxaliplatin, Src homology-2 domain-containing protein tyrosine phosphatase-2 can inhibit DNA repair by dephosphorylating poly (ADP-ribose) polymerase (PARP)-1, which induces cytosolic dsDNA accumulation and then triggers this pathway in CRC (196). Specific compounds, including G-quadruplex ligand TMPyP4, lovastatin and riluzole, also drive the cGAS-STING pathway by inducing DNA damage, leading to CRC regression (197-199). Similarly, radiotherapy-caused DNA damage triggers cGAS-STING activation within malignant cells, enhancing the antitumor immune response in CRC (200). Supporting this, radiotherapy-sensitive regions in MC38 models exhibit significantly higher type I IFNs compared with the treatment-resistant or untreated areas (201). Therefore, activating the cGAS-STING

pathway effectively improves radiotherapeutic efficacy in CRC (202,203). Notably, serine/methionine restriction has been shown to activate tumor cell-intrinsic cGAS-STING signaling, hindering CRC development (204,205), indicating that amino acid metabolism may also be involved in the regulation of cGAS-STING activity in CRC.

Currently, most evidence preliminarily supports an antitumor effect of the tumor cell-intrinsic cGAS-STING pathway in CRC. Therefore, activating tumor cell-intrinsic STING signaling holds promise for the treatment of this disease. Accordingly, two major therapeutic strategies can be used to activate this pathway in CRC: Reversing intrinsic suppression, such as targeting inhibitory factors (including HER2, KAT6A and TREX1), and extrinsically activating the pathway via DNA-damaging therapies. Combination therapy may be particularly effective since it couples activation of this pathway with enhanced antigen release, immune cell recruitment or checkpoint blockade. For example, the combination of oxaliplatin with curcumin, chemotherapy with DNA repair inhibitors and radiotherapy with CD73 blockade can strengthen cGAS-STING signaling and improve antitumor immunity (159,206,207). Other compounds, including nilotinib and the G-quadruplex stabilizer CX-5461, have also been reported to inhibit CRC through this pathway (208,209).

Nevertheless, these therapeutic implications should be interpreted in the context of the aforementioned cellular heterogeneity. Although restoring tumor cell-intrinsic cGAS-STING signaling may transform immune-cold CRC into a more immune-responsive state and enhance the sensitivity to ICIs, the non-selective or persistent activation of STING may have different effects on T cells, macrophages and stromal cells. Therefore, cGAS-STING-targeted therapies for CRC may need to consider tumor molecular subtypes, cellular compartments, the source and intensity of activation signals and the TME.

4. Strategies for activating the cGAS-STING pathway and their therapeutic applications

Clinical translations and limitations of direct cGAS-STING agonists in cancer treatment. According to the review by Tian *et al* (210), the direct agonists of cGAS-STING can be organized into the following six classifications: Metal ions (such as Mn²⁺ and Zn²⁺), small molecule agonists (including DMXAA, diANZi and MSA-2), protein-based agents (such as polyglutamine binding protein-1 and recombinant STING protein), nucleic acid-based compounds (such as cyclic dinucleotides), chitosan and ionizable lipids. Supporting this, studies show that Mn²⁺ ions and cyclic dinucleotides significantly improve the function of NK cells via cGAS-STING activation, especially against major histocompatibility class I deficient tumors (211,212). Similarly, low-dose STING agonist ADU-S100 can potentiate sustained antitumor function of CD8⁺ T cells (183). These reports suggest that activating the cGAS-STING pathway may enhance antitumor immunity.

Several early-phase clinical trials have evaluated or are evaluating activation of the cGAS-STING pathway for cancer treatment. The Phase I trial of ulevostinag (NCT03010176) in patients with advanced solid tumors or lymphomas has been

completed (213). Ulevostinag demonstrated STING activation and a general safety profile, although its antitumor activity was limited (213). The Phase I trial of ADU-S100 (NCT02675439) in advanced solid tumors or lymphomas was terminated since no substantial antitumor activity was observed, with only 1 confirmed partial response among 47 patients (214). The Phase I/II trial of IMSA101 (NCT04020185) in advanced solid tumors has also been completed. No objective responses were observed with IMSA101 monotherapy, while limited activity was observed in combination with ICIs (215). Other studies include the ongoing Phase I trial of CRD3874-SI (NCT06021626), the completed Phase I trials of SB 11285 (NCT04096638) and BMS-986301 (NCT03956680) and the terminated Phase I trial of SNX281 (NCT04609579). The SNX281 trial was terminated due to a sponsor decision unrelated to safety concerns.

In gastrointestinal cancer types, several clinical trials have been performed to investigate the possibility of activating the cGAS-STING pathway to treat tumors. NCT06824064 is an ongoing Phase II study of RBS2418 in patients with advanced CRC. RBS2418 inhibits ectonucleotide pyrophosphatase/phosphodiesterase 1 and prevents the degradation of extracellular 2'3'-cGAMP, thereby enhancing STING signaling (216). NCT04420884 is a completed Phase I/II study of dazostinag (TAK-676) alone or in combination with pembrolizumab in advanced solid tumors, including CRC. Dazostinag plus pembrolizumab showed preliminary antitumor activity in recurrent/metastatic squamous cell carcinoma of the head and neck, although CRC-specific efficacy data remain limited (217). The Phase I study of E7766 (NCT04144140) in advanced solid tumors or lymphomas was terminated due to a sponsor business decision unrelated to safety or clinical activity. Among 24 treated patients, 8 achieved stable disease, but no objective responses were observed (218). The Phase I/II study of TAK-500 (NCT05070247) was terminated after the clinical futility criterion was met, and the planned dose-expansion phase was not initiated. Overall, these studies suggest that activation of the cGAS-STING pathway remains at an early stage of clinical development. Although pharmacological activation of this pathway has shown target engagement and generally acceptable safety profiles, clinical antitumor responses remain limited. Detailed information on the study phase, clinical status, tumor types and key clinical findings is summarized in Table I.

Notably, the cGAS-STING pathway is not restricted to tumor cells, and alterations in STING activity have distinct consequences in normal tissues. Loss of STING impairs cytosolic DNA sensing and type I IFN responses, thereby compromising antimicrobial host defense and increasing susceptibility to infection. In the STING-associated vasculopathy with onset in infancy, gain-of-function mutations in STING1 can cause serious systemic inflammation, skin vasculopathy and interstitial lung diseases (219,220). Systemic administration of STING agonists may also affect normal tissues and cause excessive inflammatory responses, including acute inflammation and cytokine storm (221). Therefore, systemic administration of cGAS-STING agonists to patients with cancer may have some side effects. Finding a balance between dosage, efficacy and side effects is crucial for the clinical application of STING agonists in cancer treatment.

As aforementioned, specifically activating the cGAS-STING signaling pathway in tumor cells or antitumor immune cells may maximize their antitumor effects while minimizing adverse reactions.

Strategies to activate tumor cell-intrinsic cGAS-STING signaling. Current strategies to activate the intrinsic STING signaling in tumor cells center on a few core principles (Fig. 4). Firstly, the most classic approach involves using traditional chemoradiotherapy to induce DNA damage and cytoplasmic DNA accumulation (such as micronuclei and mtDNA), thereby activating related pathways and triggering the release of type I IFNs and inflammatory cytokines to reshape the TME (53,56). Furthermore, inhibiting DNA damage repair can enhance radiotherapy-induced activation of the cGAS-STING pathway (106). Secondly, the direct application of cGAS-STING pathway agonists, such as small-molecule compounds or metal ions (including Mn^{2+}), provides a method for directly activating this pathway (88,140,157). Thirdly, developing targeted strategies to address the intrinsic mechanisms by which tumor cells suppress the cGAS-STING pathway may be key to restoring its sensitivity, such as targeting inhibitory factors that promote cGAS/STING protein degradation, blocking nucleases that clear cytosolic DNA and regulating key points in signal transduction (60,79,86,124,161). The main goal of these strategies is to remove the tumor cells' own restrictions on this pathway.

Notably, although inhibition of DNA damage response pathways, such as PARP and ataxia telangiectasia and Rad3-related protein (ATR), may increase DNA damage and promote cGAS-STING activation in tumor cells, this strategy may also affect normal tissues. These pathways are important for DNA repair in normal cells, and their inhibition may increase normal-tissue toxicity, especially when combined with radiotherapy or other DNA-damaging treatments. Early clinical studies show that combining PARP or ATR inhibitors with radiotherapy has obvious hematologic and site-specific normal-tissue toxicities (222,223). Therefore, these strategies should comprehensively consider the balance between the efficacy and side effects.

Cell-specific delivery and combinatorial therapeutic strategies. Developing a tumor-targeted or cell-specific delivery platform may improve therapeutic precision and reduce systemic toxicity. Several strategies, such as nanoparticle carrier systems and cyclic dinucleotide-manganese particles, may enhance the targeting and local dosage of cGAS/STING agonists, thereby improving efficacy and reducing side effects (224,225). However, most of these approaches are still in the preclinical stage and further work is needed to improve tumor delivery, cellular targeting and safety. The development of these strategies will contribute to the clinical application of cGAS/STING agonists in cancer treatment.

In addition, designing combination strategies may effectively enhance the efficacy of cGAS-STING pathway activation by overcoming the immunosuppressive TME, such as pairing STING agonists with ICIs, targeted metabolic drugs or other immunomodulators (68,130,207). Several studies have

Table I. Clinical trials evaluating the efficacy of cGAS/STING agonists in cancer treatment.

Clinical trial	Agent	Phase/current status	Tumor type(s)	Key clinical findings
NCT03010176	Ulevostinag	Phase I/ Completed	Advanced/metastatic solid tumors or lymphomas	Ulevostinag showed STING activation and was generally well tolerated. Pyrexia was the most common adverse event (70%), and 10 patients had dose-limiting toxicities. The recommended Phase II dose was 540 μ g.
NCT02675439	ADU-S100	Phase I/ Terminated	Advanced/metastatic solid tumors or lymphomas	ADU-S100 was generally tolerated, but its antitumor effect was limited. Among 47 patients, only 1 confirmed partial response was observed.
NCT04020185	IMSA101	Phase I/II/ Completed	Advanced treatment-refractory malignancies	Among 40 patients, IMSA101 was generally well tolerated, but no objective responses were observed with IMSA101 monotherapy.
NCT06021626	CRD3874	Phase I/ Recruiting	Advanced/metastatic solid tumors	Safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy are being evaluated. Currently, no clinical results have yet been reported.
NCT04096638	SB 11285	Phase I (1a/1b)/ Completed	Advanced solid tumors	Currently, formal clinical efficacy results have not yet been reported.
NCT03956680	BMS-986301	Phase I/ Completed	Advanced solid tumors	Currently, formal clinical efficacy results have not yet been reported.
NCT04609579	SNX281	Phase I/ Terminated	Advanced solid tumors and lymphoma	The trial was terminated following a sponsor decision not related to safety concerns. No formal efficacy results have been posted.
NCT06824064	RBS2418	Phase IIa; Recruiting	Advanced, metastatic, and progressive CRC	The study is ongoing, and clinical efficacy and safety results have not yet been reported.
NCT04420884	Dazostinag	Phase I/II / Completed	Advanced/metastatic solid tumors	Dazostinag combined with pembrolizumab showed preliminary antitumor activity in patients with recurrent/metastatic squamous cell carcinoma of the head and neck. Currently, clinical efficacy data in colorectal cancer have not yet been reported.
NCT04144140	E7766	Phase I/1b/ Terminated	Advanced solid tumors or lymphomas	Pharmacodynamic analyses demonstrated on-target STING-associated immune activation. Among 24 patients, 8 (33.3%) achieved stable disease as their best response. The trial was terminated due to a sponsor business decision unrelated to safety or clinical activity.
NCT05070247	TAK-500	Phase I/II/ Terminated	Advanced/metastatic solid tumors	The trial enrolled 61 patients and was terminated as the criterion for clinical futility of TAK-500 was met.

STING, stimulator of interferon genes; CRC, colorectal cancer.

demonstrated that activating tumor cell-intrinsic cGAS-STING signaling can enhance the efficacy of ICIs in digestive system cancer types (68,142,171,179,206). A study has also shown that cGAS expression in tumor cells is essential for an effective response to PD-L1 blockade (226). By contrast, the loss of either cGAS or STING in tumor cells or inhibiting that activation of this pathway can lead to resistance to ICIs (79,81,227). These reports suggest that impaired cGAS-STING signaling

may represent an important mechanism of ICI resistance in cancer treatment.

However, the relationship between cGAS-STING activity and immunotherapy efficacy is not simply a positive correlation. STING activation can promote antitumor immunity but also induce compensatory PD-L1 expression. This resistance may be partly overcome by combining STING agonists with PD-1/PD-L1 blockade (66,228). Beyond PD-L1,

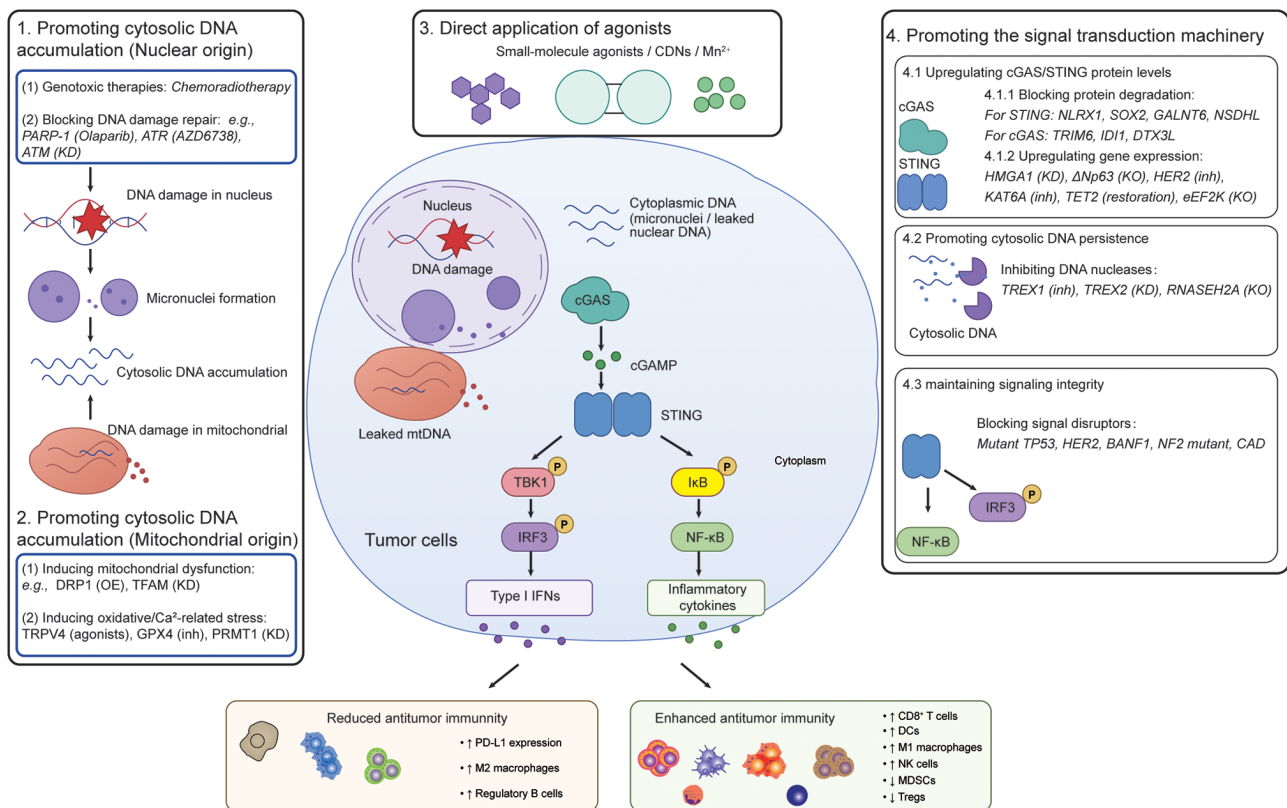


Figure 4. Strategies to activate the cGAS-STING pathway. Tumor cells frequently suppress the cGAS-STING pathway through multiple mechanisms. Several strategies can be used to restore or enhance this pathway. Firstly, genotoxic therapies or inhibiting DNA damage repair, such as chemoradiotherapy and targeting PARP-1, can promote nuclear DNA damage and cytosolic DNA accumulation, which then activates this pathway. Secondly, mitochondrial dysfunction or oxidative/Ca²⁺-related stress can trigger mitochondrial DNA damage and leakage, providing an additional source of cytosolic DNA for this pathway activation. In addition, direct administration of STING agonists, including small-molecule agonists, CDNs, and Mn²⁺, can bypass insufficient endogenous DNA sensing and directly enhance pathway activation. Meanwhile, cGAS-STING signaling can be reinforced by upregulating cGAS/STING protein levels and by maintaining cytosolic DNA persistence and downstream signaling integrity. Collectively, these approaches enhance cGAS-STING signaling, which activates the TBK1-IRF3 and NF-κB pathways to produce type I IFNs and inflammatory cytokines, resulting in TME remodeling to influence antitumor immune responses. Notably, DNA damage repair inhibition can also increase hematologic and normal-tissue toxicities, especially when combined with radiotherapy or other DNA-damaging therapies. CDNs, cyclic dinucleotides; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; IRF3, IFN regulatory factor 3; IκB, inhibitor of κB; NF-κB, nuclear factor κB; OE, overexpression; KD, knockdown; inh, inhibition.

radiation-induced DNA damage also upregulates the expression of CD73 in tumor cells. CD73 promotes the production of extracellular adenosine, which suppresses the activity of CD8⁺ T cells and NK cells (229). Thus, CD73 may act as a negative feedback mechanism that limits cGAS-STING-mediated antitumor immunity (77,126). These findings provide a rationale for combining STING agonists with ICIs, CD73 blockade or other strategies targeting immunosuppressive feedback pathways.

cGAS-STING activation can promote the production of multiple chemokines, which then facilitate the infiltration of immune cells. Adoptive cell therapies, such as chimeric antigen receptor (CAR)-T and CAR-NK cells, have shown potent activity in digestive system cancer types (230,231). However, limited intratumoral infiltration of CAR-T and CAR-NK cells has always been a factor restricting their efficacy. Preclinical studies demonstrate that cGAS-STING activation can potentiate the efficacy of CAR-T cells against multiple solid tumors, including lung, renal and cervical cancer (232-234). STING activation can also enhance CAR-T function through cytokine signals such as IL-18 (235). Similarly, cGAMP administration improves the function of CAR-NK cells in the treatment of pancreatic cancer (143).

Cell-type-specific considerations and future directions. Although STING activation in tumor cells or some cell components in the TME may enhance the recruitment of immune cells and antitumor immunity, directly activating STING in T cells may have unfavorable effects. Previous studies have shown that STING activation in T cells could inhibit the proliferation of T cells and induce the metabolic dysfunction of T cells (236,237). More notably, a recent study showed that although pharmacological STING activation in the tumor enhances antitumor immunity, STING signaling in CAR-T cells limits their therapeutic efficacy (238). Combining STING-deficient CAR-T cells with the STING agonist diABZI can more effectively control tumor progression (238). These findings suggest that STING activation at the tumor site may promote the infiltration of antitumor immune cells and improve the efficacy of cell-based therapy. However, excessive STING activation in T cells or CAR-T cells may impair their function and contribute to treatment resistance.

Notably, the cGAS-STING pathway functions differently across various immune cells. Given the cell type specificity of this pathway, precise targeting is required to maximize therapeutic efficacy and minimize side effects. It may be more

effective for tumor control to activate STING in tumor cells or in selected cell types of the TME, while avoiding excessive activation in effector T cells. Single-cell sequencing technology provides a unique perspective for exploring the tumor immune microenvironment (239), which may help identify the cell populations that should be targeted or protected after cGAS-STING activation. For tumors with low or defective cGAS-STING activity, restoration or activation of this pathway may improve sensitivity to immunotherapy. By contrast, tumors with persistent or chronic STING activation may require biomarker-guided therapeutic approaches rather than further pathway activation.

Overall, future studies should focus on more precise activation of the cGAS-STING pathway in specific cell types. More optimal delivery strategies and rational combination therapies may help improve antitumor efficacy of cGAS-STING activation. Notably, achieving a balance between therapeutic efficacy and toxicity will be essential for the clinical application of cGAS-STING-based therapies.

5. Discussion and conclusions

Activating the cGAS-STING pathway in tumor cells, DCs and NK cells can promote antitumor immunity. However, the available evidence also demonstrates the protumor effects of this pathway in specific cellular and disease contexts, such as promoting tumor cell metastasis and inducing M2 macrophages and regulatory B cells. Further investigation into the underlying causes of these heterogeneities will enhance our understanding of the cGAS-STING signaling pathway in digestive system cancer types, ultimately enabling more effective harnessing of its functions against cancer.

On the one hand, cGAS-STING pathway activation in tumor cells may enhance the malignant phenotypes of tumor cells, such as promoting EMT and stemness. In tumor cells with high chromosomal instability (CIN), the cGAS-STING pathway is constitutively activated as a result of ongoing chromosomal segregation errors and compromised nuclear integrity (240,241). CIN-driven chronic STING activation can lead to STING-specific type I IFN tachyphylaxis, alongside a signaling switch toward the non-canonical NF- κ B pathway and the induction of endoplasmic reticulum stress (241,242). RelB/p52-dependent non-canonical NF- κ B signaling has been shown to promote EMT, invasion and metastasis in tumor cells (241). Meanwhile, CIN-triggered cGAS-STING pathway activation also promotes tumor cell survival through the IL-6-STAT3 pathway (243). STAT3 activation can maintain cancer stemness (119). Chronic STING-dependent endoplasmic reticulum stress has been shown to promote the expression of CCL2, CXCL1 and IL-11 in tumor cells to mediate a pro-metastatic TME enriched with immunosuppressive myeloid cells (242). Tumor cell autonomous processes (including EMT, stress adaptation and stem cell-like phenotypes) and non-cellular autonomous mechanisms mediated by STING-dependent secretion and TME remodeling can synergistically enhance the invasiveness and metastatic ability of tumor cells, ultimately promoting metastasis.

On the other hand, tumor cell-intrinsic pathway activation induces the expression of type I IFNs and pro-inflammatory mediators, which facilitates the infiltration of multiple

immune cells and remodels the TME. Among these immune cells, cGAS-STING activation can promote the infiltration and function of CD8⁺ T cells, NK cells and DCs, and reduce the activity of Tregs, thereby suppressing the progression of tumors. However, the effect of this pathway in macrophages remains unclear. The cGAS-STING pathway is activated in both M1-like pro-inflammatory macrophages and M2-like immunosuppressive macrophages. For macrophage polarization, this pathway may not be a switch that determines the polarization direction of macrophages, but rather a signaling hub that transmits diverse signals that affect the polarization state of macrophages. Enhanced TBK1-IRF3- type I IFN signaling and the cGAS-STING-TBK1-STAT6 pathway can drive macrophage polarization toward the M1 and M2 phenotypes, respectively (244,245). Therefore, macrophage polarization is not dictated by STING activation itself, but rather by STING-related downstream signaling. Additionally, factors that activate STING may also influence macrophage polarization. For example, direct stimulation of STING in macrophages with 2'3'-cGAMP or pharmacological agonists promotes the shift of M2 macrophages toward an M1 phenotype (244,246). Conversely, phagocytosis of tumor-derived microparticles induces M2 macrophage polarization through the cGAS-STING-TBK1-STAT6 signaling axis (245). Therefore, cGAS-STING signaling likely functions as a context-dependent signaling hub, and its impact on macrophage phenotype may depend on different downstream pathways. However, the macrophage-intrinsic cGAS-STING pathway undoubtedly affects antitumor immunity. Determining how and when this pathway is regulated in macrophages will be key to realizing its therapeutic potential.

Meanwhile, the effects of pathway activation are influenced by tumor molecular subtypes, disease stage and activating factors. In dMMR gastric and colorectal cancer, the activity of the cGAS-STING pathway is positively associated with tumor mutational burden, CD8⁺ T cell infiltration and therapeutic response to ICIs, while elevated cGAS/STING expression activity has also been reported in these tumors (8,9,152). Substantial evidence suggests that the tumor cell-intrinsic STING signaling activation is consistently linked to improved patient outcomes and stronger antitumor immunity. However, high tumor mutational burden and neoantigen load can also contribute to antitumor immunity in dMMR/MSI-H cancer types. Therefore, the favorable response to ICIs in patients with dMMR/MSI-H may be related to the increased tumor mutational burden and cGAS-STING activity.

Evidence shows that genomic instability can induce the exposure of genomic DNA to the cytoplasm and then activate the cGAS-STING pathway (240,241). dMMR can also promote cytosolic DNA accumulation and cGAS-STING activation (227,247). Recent research has further shown that MSI-related cytosolic DNA, enriched in a specific G-quadruplexes structure, can effectively promote cGAS-STING pathway activation and CD8⁺ T cell function in CRC (248). Collectively, these studies indicate that genomic instability associated with dMMR may promote cytosolic DNA accumulation, providing a possible mechanistic link between genomic instability and cGAS-STING activation. However, current evidence cannot fully confirm that cGAS-STING pathway activation is a necessary mediator for the response

to ICIs in patients with dMMR GC or dMMR CRC. The specific contribution of the genomic instability-cytosolic DNA-cGAS-STING axis to the efficacy of ICIs remains to be further elucidated.

While activating the cGAS-STING pathway in tumor cells represents an attractive therapeutic strategy in the treatment of digestive system cancer types, it may still confront several challenges. For example, systemic administration of STING agonists may activate this pathway in normal tissues and cause cytokine-mediated inflammation or other off-target toxicities. Activation of this pathway can also induce PD-L1 expression in tumor cells and the M2 polarization of macrophages, which may self-limit its effectiveness (66,135). Furthermore, by employing multiple mechanisms to dampen this pathway, tumor cells may develop resistance to therapeutic strategies designed to activate it. To improve the utilization of the anti-tumor effects of this pathway, further in-depth research may be needed to address these challenges.

Collectively, the effect of cGAS-STING pathway activation on tumors cannot be defined simply as tumor suppressive or tumor promoting, and should be considered comprehensively based on the tumor type and cellular compartments. Although tumor-intrinsic cGAS-STING activation represents a promising therapeutic avenue to suppress tumor progression by enhancing antitumor immunity in digestive system cancer types, the application of cGAS-STING activation cannot be considered from the perspective of tumor cells alone. A net therapeutic benefit is likely achievable only with cell-type-restricted delivery, whereas untargeted activation carries a real risk of net harm that extends beyond 'off-target toxicity'. Untargeted pathway activation may, in some contexts, promote immunosuppression or tumor progression, to reinforce the rationale for cell-type-selective therapeutic strategies. Developing precision strategies to stimulate this pathway in specific cell populations, particularly in DCs and NK cells, may potentiate the control of tumors. Therefore, future treatment strategies may need to clearly define when, where and in which cell the pathway is activated, and utilize synergistic strategies to enhance efficacy and reduce adverse reactions.

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TC, DH and HY collected related papers and wrote the original manuscript. TC, JZ, JS and HZ contributed to the figures. HY, DH and HZ designed the study. TC, JZ, JS, HY, DH and HZ revised the manuscript. All authors contributed to the article.

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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