



EDITORIAL

Harnessing the STING pathway for HCC treatment

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The cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS-STING) pathway has significantly deepened our knowledge about innate immune sensing. The cGAS-STING pathway was originally identified as having a role in detecting cytosolic deoxyribonucleic acid (DNA) for stimulating antiviral responses. Recently, the cGAS-STING pathway has increasingly been acknowledged to be important in tumor immunology with deterministic roles in cancer progression and therapeutic responses. This review will discuss the molecular mechanisms underlying cGAS-STING signaling, the paradoxical roles in cancer progression and suppression, and the relevance and translational potential of targeting this pathway, especially in the context of hepatocellular carcinoma (HCC). Emerging research directions and therapeutic strategies that leverage cGAS-STING activation to enhance anti-tumor immunity will also be highlighted.

cGAS-STING pathway

The cGAS-STING pathway is an evolutionarily conserved mechanism that detects viral DNA and triggers an immune response to protect the host. cGAS packages cytosolic DNA into cGAMP. cGAMP accumulation activates STING in the endoplasmic reticulum (ER). STING moves to the Golgi apparatus where it dimerizes and oligomerizes, recruiting

TANK-binding kinase 1 (TBK1). STING binding to TBK1 leads to autophosphorylation of TBK1 and phosphorylation of STING. The STING-TBK1 complex mediates binding and dimerization of IRF3, which translocates into the nucleus to mediate the type 1 interferon (IFN) response. In addition, the STING pathway activates nuclear factor kappa B (NF- κ B), which transcriptionally activates a series of inflammatory cytokines to elicit immune responses. The underlying mechanism has been previously described in more detail¹. A recent study showed that adenylosuccinate lyase (ADSL) has a critical role in regulating STING activity. Hypoxia-mediated inhibitory kappa B kinase beta (IKK β) promotes ADSL phosphorylation, enabling an interaction with STING in the ER. ADSL generates fumarate, which blocks the interaction of cGAMP with STING. Treatment with an ADSL ER translocation blocking peptide was reported to effectively activate STING and impede tumor growth and enhance anti-tumor efficacy of anti-programed death-1 (PD-1) in murine breast cancer models with increased infiltration and effector functions of CD4⁺ T, CD8⁺ T, and natural killer (NK) cells. Clinically, ADSL T350 phosphorylation is also associated with poor clinical outcome in breast cancer patients².

cGAS-STING activation in cancer

The cGAS-STING pathway is frequently activated in cancer. Herein we summarize several underlying reasons for an abnormal presence of DNA in the cytosol of cancer cells (**Figure 1**). First, defects in DNA damage response (DDR) are common in cancer, leading to the generation of DNA breaks and fragments that can leak into the cytoplasm³⁻⁶. Furthermore, cancer treatment (e.g., radiation)⁷ and DNA repair inhibitor [e.g., poly(ADP-ribose) polymerase (PARP) inhibitors] induce additional DNA damage, augmenting DNA fragment leakage into the cytoplasm⁸⁻¹⁰. Second, extrachromosomal DNA

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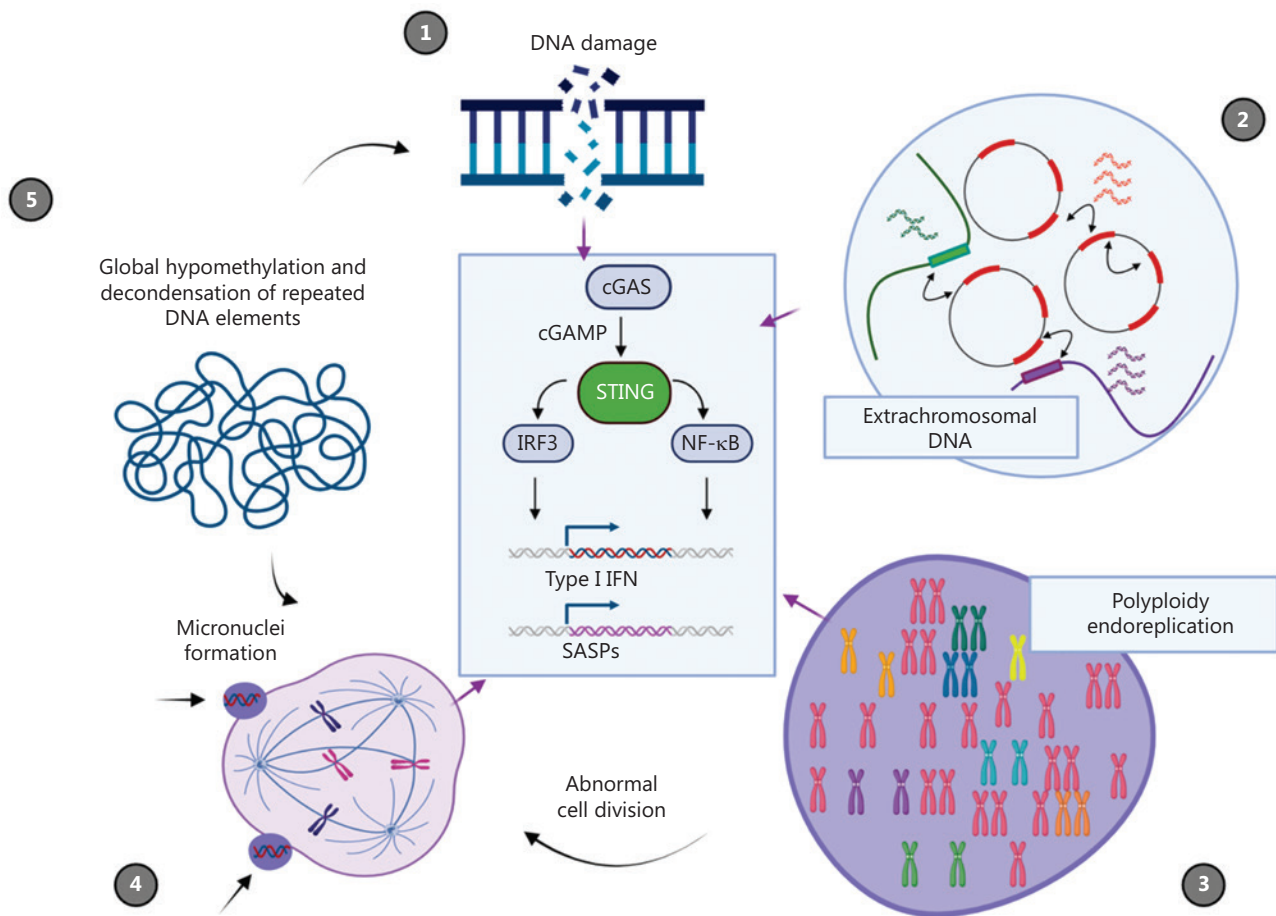


Figure 1 Genomic instability triggers cGAS-STING signaling through cytosolic DNA accumulation. The cGAS-STING pathway serves as a cytosolic DNA sensor, initiating type I IFN and NF- κ B-mediated inflammatory responses. This pathway is frequently activated in cancer through multiple mechanisms, which lead to cytosolic DNA accumulation. These mechanisms include the following: (1) defective DNA damage response and therapy-induced DNA damage generating DNA fragments; (2) presence of extrachromosomal DNA; (3) polyploidy-induced chromosome mis-segregation; (4) abnormal cell division producing micronuclei; and (5) epigenetic deregulation, which causes decondensation of repeated DNA elements and leads to DNA damage and micronuclei. Collectively, these diverse pathways of genomic instability converge to activate the cGAS-STING signaling pathway in cancer cells. cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; DNA, deoxyribonucleic acid; IFN, interferon; IRF3, interferon regulatory factor 3; NF- κ B, nuclear factor kappa B; SASPs, senescence-associated secretory phenotypes; STING, stimulator of interferon genes.

(ecDNA) is another source because ecDNA is within the cytosol of cancer cells¹¹. Third, polyploidy and other nuclear abnormalities in cancer cells cause mis-segregation of chromosomes, further contributing to micronuclei formation and cytosolic DNA accumulation¹². Fourth, cancer cells undergo abnormal cell division, which leads to micronuclei formation, and small extranuclear bodies containing chromosomal fragments are within cancer cells¹³. Fifth, another important contributing factor of cGAS-STING activation in cancer is aberrant epigenetic deregulation, such as global DNA hypomethylation, which might cause decondensation of repetitive

elements, leading to DNA damage and micronuclei formation¹⁴. All these processes could independently or collectively activate the cGAS-STING pathway in cancer cells.

Tumor suppressive and oncogenic roles of cGAS-STING

The most prominent anti-tumor effect of cGAS-STING is mediated through the production of type I IFNs, which activate dendritic cells (DCs), tumor-associated macrophages

(TAMs), T cells, and NK cells within the tumor microenvironment (TME). STING signaling in DCs enhances antigen presentation capacity by promoting cross-presentation to CD8⁺ T cells, thereby priming cytotoxic T cells. Upon activation of cGAS-STING, the major histocompatibility complex (MHC) molecules and co-stimulatory molecules on TAMs, such as CD80 and CD86, are upregulated, which enhances the ability to activate cytotoxic T cell. Furthermore, IFN-stimulated secretion of chemokines, like C-X-C motif chemokine ligand 10 (CXCL10), facilitates NK cell recruitment and activation^{15,16}. STING also activates NF- κ B-dependent cytokine signaling to mediate the anti-tumor response, which shapes a pro-inflammatory TME and recruits a wide range of immune cells, such as TAMs. In addition to a role in immune cells, STING is expressed in cancer cells to elicit anti-tumor effects. Generally, cGAS-STING induces cancer cell senescence and promotes the secretion of senescence-associated secretory phenotypes (SASPs), such as interleukin (IL)-6/8, for immune clearance. Furthermore, STING activates autophagy to trigger cell death by triggering LC3-associated phagocytosis in tumor cells, leading to lysosomal degradation. More general functions of cGAS-STING have been thoroughly described elsewhere¹⁶. Specific findings will be elaborated within the next section in the context of liver cancer. Most of the current findings suggest that the cGAS-STING pathway suppresses cancer development. In addition, some studies have shown that the cGAS-STING pathway elicits persistent inflammation, which promotes cancer. STING-deficient mice are less prone to cancer development in a cutaneous cancer model¹⁷. cGAS-STING also promotes non-canonical NF- κ B pathway, which fosters a pro-inflammatory yet immunosuppressive tumor microenvironment by recruiting immunosuppressive cells. Tumor necrosis factor- α (TNF- α) and IL-6 recruit immunosuppressive TAMs, which subsequently secrete IL-10, transforming growth factor- β (TGF- β), and arginase-1 to suppress T cell cytotoxicity. Recruitment of myeloid-derived suppressor cells (MDSCs) through C-C motif chemokine ligand (CCL)2/CCL5 lead to CD8⁺ T and NK cell suppression *via* arginase-1 and programmed death-ligand 1 (PD-L1). Furthermore, chronic secretion of TNF- α and IL-6 induces inhibitory molecules [e.g., PD-1, T cell immunoglobulin and mucin domain containing 3 (TIM3), and lymphocyte-activation gene-3 (LAG-3)] on T cells, driving CD8⁺ T cells into a dysfunctional or exhausted state¹⁸. Another important finding showed that over-activation of the cGAS-STING pathway increases expression of ER stress and cell death pathways, promoting T cell

exhaustion and apoptosis¹⁹. Interestingly, a study showed that tumor induces STING-mediated cell death in T cell to bypass immune surveillance²⁰.

STING activation in hepatocarcinogenesis

Hepatitis B virus (HBV) infection and metabolic dysfunction-associated steatotic liver disease [MASLD (formerly NAFLD)] are two major etiologic drivers of HCC, where the STING signaling pathway exhibits a dual role by eliciting persistent inflammation and mediating anti-tumor responses, as described previously. The paradoxical role of the cGAS-STING pathway makes HCC an ideal model to dissect the context-dependent effects of STING activation, such as in the context of HBV or MASLD. Recent studies have illuminated how the cGAS-STING pathway is involved in these contexts, shaping the inflammatory and immune landscape of the liver, and thereby influencing tumorigenesis.

cGAS expression is barely detectable in HCC, whereas STING is present in most HCC cell lines^{21,22}. The mechanisms underlying cGAS silencing in HCC have not been established. Whether cGAS loss contributes to the ability of HBV to evade cGAS-STING-mediated clearance has not been established. Interestingly, our previous studies demonstrated that DEAD-box helicase 41 (DDX41) rather than cGAS is the cytosolic DNA sensor in HCC cells. Our studies showed that DDX41-STING is a common mechanistic pathway through which novel and potent cell cycle inhibitors of polo-like kinase 4 (PLK4) (CFI-400945) and threonine and tyrosine kinase (TTK) (CFI-402257) disrupt crucial processes in centrosome duplication and spindle assembly checkpoint, respectively, resulting in extensive genomic instability, DNA damage, and the formation of micronuclei (**Figure 2**). Interestingly, PLK4 blockade results in endoreplication in which DNA duplication continues in the absence of cell division, leading to extensive amount of DNA trapped in the cytosol (16N). Although cGAS is inhibited during cell division, HCC cells leverage DDX41 as the cytosolic DNA sensor. This finding might provide a reason why STING is highly activated by a PLK4 inhibitor. In addition, TTK blockade did not result in endoreplication but led to incorrect chromosome segregation and micronuclei formation (**Figure 2**). All of the abovementioned events stimulate the DDX41-STING pathway in HCC cells. Activation of the STING pathway leads to the production of type I IFN

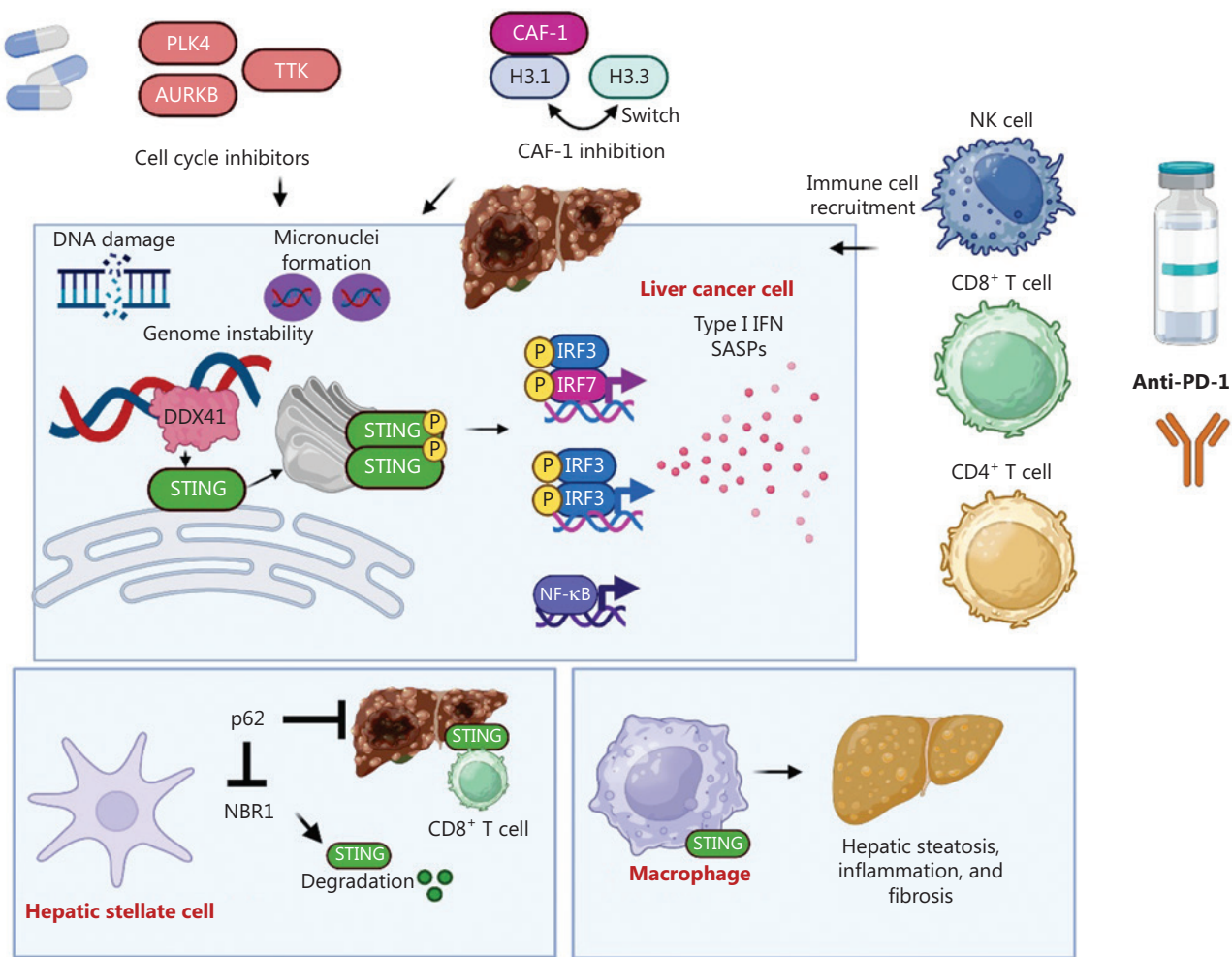


Figure 2 Activation of STING signaling in HCC and MASLD. The STING pathway is activated in HCC by cytosolic DNA sensing *via* DDX41. Cell cycle inhibitors, such as PLK4, TTK, or AURKB, induce genomic instability and micronuclei formation, triggering DDX41-STING signaling to elicit IRF3/7/NF- κ B responses, which recruit anti-tumor immune cells, such as CD4⁺ T, CD8⁺ T, and NK cells. The epigenetic regulator, CAF-1, maintains chromatin stability to suppress STING activation in HCC cells, while CAF-1 knockout leads to H3.1 to H3.3 switch, which enhances genomic instability and STING-driven immunity. These approaches increase recruitment of immune cells to the tumor microenvironment and sensitize HCC to anti-PD-1 treatment. STING in myeloid cells promotes steatosis, inflammation, and fibrosis in MASLD, whereas hepatic stellate cells regulate STING stability through the NBR1/p62 axis, thus impacting CD8⁺ T cell responses and hence HCC development. Together, these microenvironmental mechanisms govern immune surveillance in HCC. CAF-1, chromatin assembly factor 1; DDX41, DEAD-box helicase 41; DNA, deoxyribonucleic acid; IFN, interferon; IRF, interferon regulatory factor; MASLD, metabolic dysfunction-associated steatotic liver disease; NBR1, neighbor of BRCA1 gene 1; NF- κ B, nuclear factor kappa B; NK, natural killer; PD-1, programmed death-1; PLK4, polo-like kinase 4; SASPs, senescence-associated secretory phenotypes; STING, stimulator of interferon genes; TTK, threonine and tyrosine kinase.

and SASP, creating a pro-inflammatory TME. This process, in turn, recruits and activates immune cell subsets, including NK, CD4⁺, and CD8⁺ T cells, which facilitate tumor clearance. Interestingly, our studies demonstrated that the IRF3/IRF7 dimeric complex and NF- κ B are responsible for the type I IFN and inflammatory cytokine transcriptional cascade^{21,22}. In another study we demonstrated that a replication-dependent

epigenetic regulator [chromatin assembly factor 1 (CAF-1)], which is a histone chaperone, is often overexpressed in HCC and protects HCC cells from STING activation. Knockout of CAF-1 depletes histone H3.1 deposition and results in H3.3 accumulation, leading to open euchromatin structure that renders susceptibility to DNA damage, formation of micronuclei, and subsequent activation of STING in HCC. Knockout of

CAF-1 in murine HCC enhances type I IFN, increases CD8⁺ T cell infiltration, and sensitizes HCC to anti-PD-1 treatment²³ (**Figure 2**).

MASLD is the most rapidly rising etiology of HCC. It has been shown that human patients with MASLD, as well as animals on high-fat diets (HFDs), display high STING expression in non-parenchymal cells compared to liver tissues²⁴. Deletion of STING in myeloid cells in mice fed a HFD specifically alleviates hepatic steatosis, inflammation, and fibrosis. This finding was reversed by transplantation of bone marrow cells from wildtype (WT) mice. STING-deficient macrophages reduce inflammatory markers in response to cGAMP and lipopolysaccharide. Co-culturing experiments with hepatocytes and hepatic stellate cells together with STING-deficient macrophages had fewer inflammatory markers in stellate cells and reduced lipid accumulation in hepatocytes²⁴ (**Figure 2**). Another interesting study showed that neighbor of BRCA1 gene 1 (NBR1) and p62 counteracted with each other in hepatic stellate cells to regulate STING stability and hence control the level of STING in HCC²⁵. It was shown that NBR1 inhibits the interaction of STING with tripartite motif containing 32 (TRIM32) to prevent STING ubiquitination. NBR1 regulates trafficking of STING from Golgi to achieve tightly controlled STING degradation. p62 interacts with NBR1 and prevents NBR1-mediated degradation of STING in hepatic stellate cells. Therefore, p62 knockout mice were reported to develop HCC, in which the phenotypes could be nullified in p62 and NBR1 double knockout mice. The p62 and NBR1 suppressing and promoting roles in HCC development are dependent on STING-mediated inflammatory responses through CD8⁺ T cells²⁵. These important microenvironment factors have detrimental roles in eliciting immune responses against tumorigenesis (**Figure 2**).

STING activating therapies in HCC

Most current studies have suggested that the cGAS-STING pathway represents an attractive target for activation in which STING is the most promising target. Translational efforts have been devoted to the development of STING agonists. The STING pathway can be indirectly activated by other mechanisms, drugs, or cancer treatments, such as radiotherapy/chemotherapy, PARP inhibitors, cell cycle inhibitors, and even epigenetic inhibitors, that can induce DNA damage, micronuclei, and mitochondrial DNA leakage. In addition to the above-mentioned PLK4 and TTK inhibitors, our group showed that

common cell cycle inhibitors, including chemo- and targeted-drugs (e.g., paclitaxel and palbociclib), are microtubule stabilizers and cyclin-dependent kinase 4/6 inhibitors, as well as aurora kinase inhibitors. Despite the differences in targeting steps in the cell cycle, these cell cycle inhibitors activate the STING pathway through DDX41 but not cGAS. These inhibitors activate the pro-inflammatory cytokines and SASPs to mediate CD4⁺ T, CD8⁺ T, and NK cell recruitment. All these inhibitors work synergistically with anti-PD-1 to suppress HCC and improve the survival outcomes of mice with aggressive HCC²⁶.

In addition, blocking nucleases, such as three prime repair exonuclease 1 (TREX1), may cause more cytosolic DNA to accumulate while blocking ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), which is involved in the hydrolysis of nucleotide triphosphates and may prevent cGAMP degradation. Both approaches are attractive therapeutic approaches for drug development aimed at activating STING.

Another category of STING agonists includes cGAMP mimics or chemicals that fit into the cyclic dinucleotide (CDN)-binding pocket of STING, such as MSA-2, which bind to STING as a non-covalent dimer to activate the pathway. Interestingly, MSA-2 is one of very few orally available STING agonists, the activity of which is further enhanced in hypoxic environments that are common in the cancer context. MSA-2 activates type I IFN and suppresses murine syngeneic colorectal tumors alone and together with anti-PD-1²⁷. The anti-tumor efficiency of MSA-2 in HCC awaits determination. There are many more on-going developments of STING agonists, which have been extensively listed in an excellent review¹⁶. Some STING agonists have advanced to clinical trials for the treatment of cancers. Most of these trials are phase I or phase I/II as monotherapy or combined treatment with immune checkpoint inhibitors. Specifically, MK-1454, ADI-S100, TAK-676, BI-1387446, BMS-986301, E7766, SNX281, HG-381, GSK3745417, exoSTING, SYN1891, SB 11285, MK-2118, and XMT-2056 are the current STING agonists being tested in clinical trials²⁸. The chemical structures, status, indications, and clinical outcomes for the immune checkpoint inhibitors are listed in an excellent review²⁸. These clinical trials should be carefully monitored to balance efficacy and safety for potential adverse effects. The optimal therapeutic window must be identified. Nevertheless, new directions are focusing on innovative approaches that enhance the delivery of STING agonists and induce an immunologically hot tumor environment for better effect using nanomaterial-based systems. RGD@Ce6@MSA-2@Liposome (RCM-Lip) is an example that uses

Table 1 Table summarizing STING activating therapies as anti-cancer treatments

Category	Mechanism of action	Examples	Combination therapy with ICB
Direct STING agonist	Binds to STING to activate IFN/NF- κ B signaling	cGAMP mimics Non-nucleotide STING agonist (e.g., MSA-2) Small molecules (e.g., MK-1454 and TAK-676)	cGAMP mimics and small molecules combined with anti-PD-1 in clinical trial
Indirect STING activators	Induce DNA damage/micronuclei to trigger STING activation	Chemotherapy/radiotherapy PARP inhibitors (e.g., olaparib) Cell cycle inhibitors (e.g., palbociclib and paclitaxel)	PARP inhibitors and cell cycle inhibitors combined with anti-PD-1 in clinical trial
Nuclease inhibitors	Block DNA/cGAMP degradation to amplify STING signaling	TREX1 inhibitors ENPP1 inhibitors	Under investigation
Nanoparticle delivery	Enhances STING agonist delivery/tumor targeting	RGD@Ce6@MSA-2@Liposome ZIF-67 nanoparticles	Combined with anti-PD-1 in clinical trial

cGAMP, cyclic GMP-AMP; DNA, deoxyribonucleic acid; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; ICB, immune checkpoint blockade; IFN, interferon; NF- κ B, nuclear factor kappa B; PARP, poly(ADP-ribose) polymerase; PD-1, programmed death-1; STING, stimulator of interferon genes; TREX1, three prime repair exonuclease 1.

liposome to package MSA-2 with a sonosensitizer (Ce6) that can trigger immunogenic cell death. RCM-Lip also includes RGD, a tumor targeting peptide to increase target precision²⁹. Another example is lipid-coated ZIF-67 nanoparticles, which simultaneously deliver cGAMP and Co²⁺ to provoke cGAS-STING and type I IFN pathways with higher drug stability and permeability³⁰. Ongoing research and clinical studies are essential to further explore and develop drugs that activate the cGAS-STING pathway, which holds significant promise for cancer therapy (Table 1).

Future direction and summary

The cGAS-STING pathway, an innate immune and traditionally anti-viral pathway, has emerged as an important pathway in restraining the development of cancer. More importantly, cGAS-STING represents an attractive pathway to be activated as cancer treatment to fully unleash the anti-tumor immune response. The STING pathway is further complicated in HCC by unique features, such as low cGAS expression, and the involvement of alternative DNA sensors, like DDX41. More cytosolic DNA sensors in addition to cGAS and DDX41 are present and need to be further investigated because the expression might be context-dependent, leading to differential responses in various cancer patients or cancer types. STING is expressed in multiple cell types. Future studies can also explore the interplay of STING in various cell types in the

TME and how this affects the TME and immune responses in HCC. In addition, how the STING pathway primes the HCC TME at early stages of hepatocarcinogenesis involving chronic inflammation caused by HBV or steatosis is another key question to be addressed. Furthermore, novel biomarkers that can help identify patients suitable for various types of drugs that activate STING are pivotal to advancing clinical trials and improving clinical benefits for these drugs. In conclusion, the cGAS-STING pathway has crucial roles in the TME and is crucial for the anti-tumor immune response. Continuous efforts are essential to further explore more therapeutic approaches that can harness this pathway and improve the clinical outcomes of HCC patients.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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