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REVIEW

Emerging Strategies for Antitumor Immunotherapy and Antiviral Defense Through the cGAS-STING Pathway

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Abstract: The cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway is a central regulator of innate immunity and plays a critical role in inducing pro-inflammatory cytokines and type I interferons (IFN-I). This pathway has emerged as a promising target for cancer immunotherapy and antiviral treatments. Despite its promise, the clinical translation of STING agonists is hindered by several challenges, including structural instability, high production costs, and inefficient delivery systems. These barriers underscore the urgent need for further research and innovation to optimize STING-based therapies. This review provides a comprehensive overview of the cGAS-STING pathway, focusing on its activation mechanisms and recent advances aimed at enhancing its therapeutic efficacy. Alternative activators of STING, including metal ions, exogenous DNA, and endogenous DNA, are discussed for their potential to stimulate this pathway. Furthermore, synergistic therapeutic strategies combining cGAS-STING activation with reactive oxygen species (ROS)-based treatments, such as photodynamic therapy, radiotherapy, sonodynamic therapy, and chemodynamic therapy, are highlighted. Finally, recent progress in harnessing STING activation for antiviral defense against emerging pathogens, such as SARS-CoV-2 and influenza viruses, is summarized to provide insights into the future development of cGAS-STING-targeted immunotherapies.

Keywords: cGAS-STING, antitumor immunotherapy, ROS-based therapy, non-ROS-based therapy, antiviral defense

Introduction

The immune system is broadly categorized into innate and adaptive immunity. The innate immune system serves as the first line of defense by recognizing pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs), thereby initiating rapid immune responses.[1–4] Among these, the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway has emerged as a central cytosolic DNA-sensing mechanism that plays a critical role in innate immunity.[5,6] STING is a key adaptor protein in DNA-triggered immune signaling and is activated by cyclic dinucleotides (CDNs).[4,7]

Subsequent studies established that cGAS functions as the primary cytosolic DNA sensor that produces cyclic GMP-AMP (cGAMP), which activates STING and induces type I interferon (IFN-I) responses. This cGAS-cGAMP-STING axis is now considered a fundamental pathway linking cytosolic DNA sensing to innate immune activation.[7] The cGAS-STING pathway plays a central role in tumor immunotherapy and antiviral defense by sensing cytosolic DNA derived from viral infection or tumor genomic instability.[8–10] Upon activation, it triggers immune responses and promotes adaptive immunity, thereby mediating immune surveillance. Given its critical role in immune activation, this pathway has emerged as a promising target for immunotherapeutic strategies.[11–14]

This review provides an overview of the activation mechanisms of the cGAS-STING pathway and summarizes current strategies for its modulation. We highlight molecular approaches to activate this pathway and discuss

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combinatorial therapeutic strategies that integrate cGAS-STING activation with tumor immunotherapy. In particular, we focus on reactive oxygen species (ROS)-mediated and non-ROS-based approaches (Figure 1). Additionally, we outline the potential of targeting this pathway for antiviral therapy.

Mechanisms of the cGAS-STING Pathway

cGAS, a key component of the STING pathway, functions as a cytosolic dsDNA sensor that is activated in a sequence-independent manner.[15–17] Under physiological conditions, host DNA is largely confined to the nucleus, and cytosolic dsDNA is typically recognized as a danger signal. It may originate from pathogens, necrotic cells, or damaged mitochondrial DNA (mtDNA).[18–20] Notably, cGAS activation depends on dsDNA length and concentration, with longer DNA fragments requiring lower concentrations for activation.[15] Binding of dsDNA to cGAS induces conformational changes that promote the formation of an active 2:2 dimer.[8]

Upon DNA recognition, cGAS catalyzes the synthesis of cGAMP, which activates STING. Activated STING translocates from the endoplasmic reticulum (ER) to the Golgi via the ER–Golgi intermediate compartment (ERGIC), where it recruits TANK-binding kinase 1 (TBK1) and forms a signaling complex. This leads to the activation of interferon regulatory factor 3 (IRF3) and nuclear factor κB (NF-κB), ultimately inducing IFN-I production and downstream immune responses.[21,22] Both exogenous and endogenous DNA can activate the cGAS-STING pathway, thereby triggering innate immune responses (Figure 2). In the tumor microenvironment, STING activation can promote immune cell infiltration, particularly of macrophages. M1 macrophages enhance antitumor immunity through IFN-I production

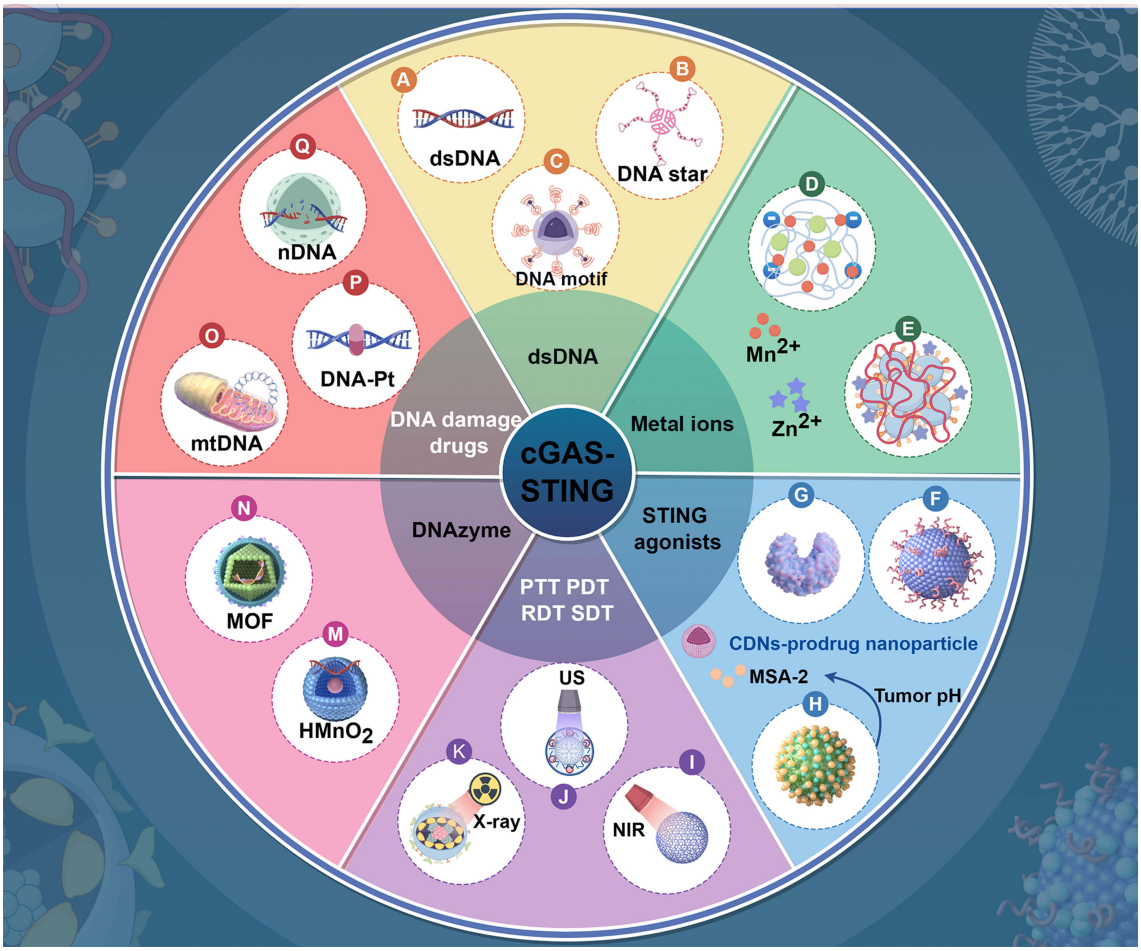

Figure 1 Schematic illustration of strategies to activate the cGAS-STING pathway for antitumor immunotherapy and antiviral defense.
Abbreviations: dsDNA, double-stranded DNA; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; DNAzyme, deoxyribozymes; US, ultrasound; MOF, metal-organic framework; PTT, photothermal therapy; PDT, photodynamic therapy; SDT, sonodynamic therapy; NIR, near-infrared light.

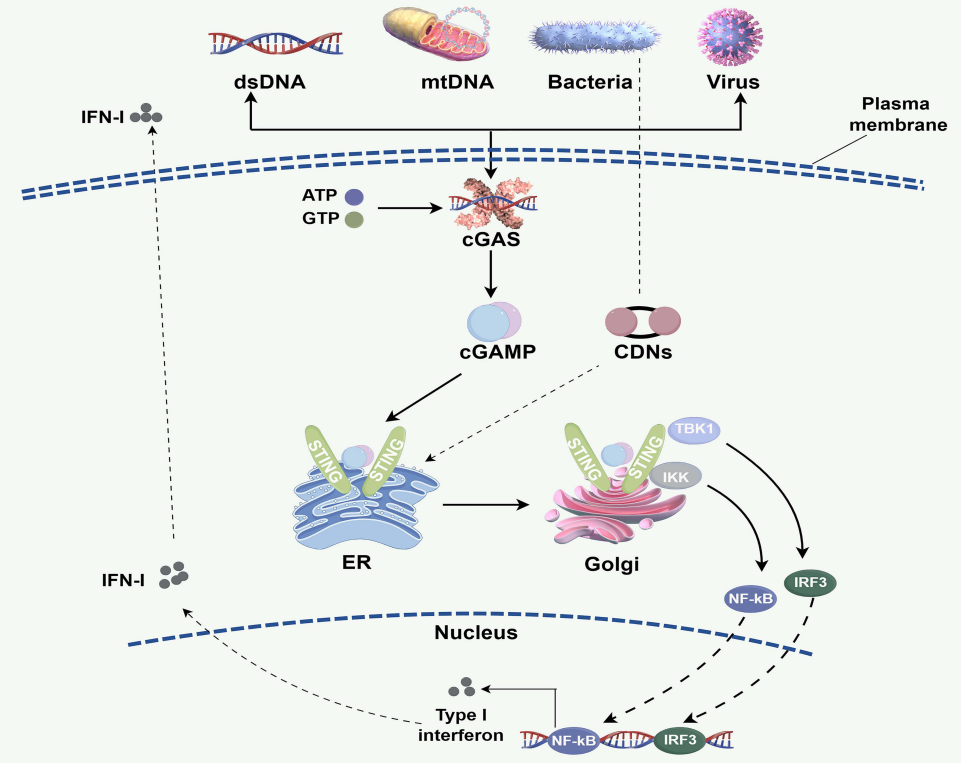

Figure 2 Mechanism of cGAS-STING pathway activation.
Abbreviations: dsDNA, double-stranded DNA; mtDNA, mitochondrial DNA; CDNs, cyclic dinucleotides; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; ER, endoplasmic reticulum; IFN-I, type I interferon.

via IRF3 and NF-κB signaling, whereas M2 macrophages exhibit immunosuppressive functions. These findings provide a mechanistic basis for STING-targeted immunotherapies.[23,24]

STING Pathway-Related Diseases

The cGAS-STING pathway is a critical component of the innate immune system, detecting cytosolic DNA and triggering the production of IFN-I and other cytokines.[25] The activation of the cGAS-STING pathway is crucial in antiviral defense and tumor therapy.[10,26–28] Upon activation, the cGAS-STING pathway triggers the release of IFN-I, which subsequently activates dendritic cells (DCs). These activated DCs then prime and activate tumor-specific $CD8^+$ T cells, establishing a key activation cascade that bridges innate and adaptive immunity while enhancing antitumor responses.[29–31] Additionally, the robust antiviral responses mediated by the cGAS-STING pathway highlight its potential as a therapeutic target for combating viral infections. This review summarizes the STING pathway and explores its promising applications in antiviral therapy.[32–37]

Overactivation of the cGAS-STING pathway has been implicated in various autoimmune diseases, in which the immune system mistakenly attacks the body's own cells (Table 1). Modulating this pathway offers a promising therapeutic approach for treating these autoimmune conditions.[38–41] Dysregulated cGAS-STING activation leads to excessive IFN-I production, resulting in autoimmune diseases driven by inflammation. Modulating or inhibiting this pathway can reduce excessive inflammation and immune responses, thereby alleviating symptoms and preventing disease progression in conditions such as systemic lupus erythematosus (SLE), Aicardi-Goutières syndrome (AGS), ischemic stroke, and STING-associated vasculopathy with onset in infancy (SAVI).[42–48] Uthaman et al developed STING-inhibiting micelles (SIMs) for the treatment of ulcerative colitis, an inflammatory condition affecting the colon.[39] Oral delivery of SIMs efficiently reduced STING expression and attenuated intestinal inflammation. Ongoing efforts to develop cGAS-STING inhibitors and modulators aim to achieve precise pathway regulation without compromising overall immune defense, offering promising options for the treatment of autoimmune and inflammatory diseases.

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Table 1 Diseases Associated with cGAS-STING Pathway

cGAS-STING	Diseases	Specific disease	Refs
Activation	Tumor	Liver metastatic colorectal cancer	[29]
		Colorectal cancer	[30]
		Advanced and metastatic breast cancers	[31]
	Antivirus	Herpes simplex virus type 1	[26]
		SARS-CoV-2	[10]
		Influenza virus	[32]
		Herpetic simplex keratitis	[33]
		Pan-influenza virus	[34]
Inhibition	Autoimmune disease	Ulcerative colitis	[39]
		Aicardi-Goutières syndrome	[44]
		STING-associated vasculopathy with onset in infancy	[40]
		Systemic lupus erythematosus	[43]
	Ischemic stroke	Subarachnoid hemorrhage	[45]
		Ischemic Penumbra	[46]
		Ischemic stroke with neuroprotection	[47]

The activation of the cGAS-STING pathway is crucial for tumor therapy and antiviral defense. While STING agonists show promise for treating infections and cancer, improper activation can lead to excessive inflammation and autoimmune responses. Further research into the mechanisms and regulation of STING activation is essential for the development of safer and more effective therapies.

Strategies to Activate the cGAS-STING Pathway

Activation of the cGAS-STING pathway is pivotal for STING-mediated tumor immunotherapy.[49–51] Besides STING agonists, a variety of activators, such as metal ions and endogenous or exogenous DNA, have been developed to efficiently activate the cGAS-STING pathway (Figure 3). These advances broaden the therapeutic prospects of this pathway.[38,52–54]

Metal Ions

In 2018, Jiang's group reported that manganese ions (Mn^{2+}) significantly enhanced the sensitivity of the cGAS-STING pathway to dsDNA, thereby improving host resistance to DNA viruses through enhanced cGAS and STING responsiveness.[55] Moreover, Mn^{2+} binding to cytosolic cGAS increases its dsDNA sensitivity and enzymatic activity, leading to increased cGAMP production even at low dsDNA concentrations.[56–58] Although Mn^{2+} is not a direct agonist of STING, it has emerged as a promising adjuvant for cGAS-STING-based tumor immunotherapy.[55,59–61] Exogenous Mn^{2+} can activate the cGAS-STING pathway, enhance antigen presentation by antigen-presenting cells (APCs), and activate natural killer (NK) cells. The combination of Mn^{2+} with anti-PD-1 boosted anticancer efficacy in various tumor models.[62,63] Immune checkpoint blockade (ICB) efficacy is often limited by immune-related adverse effects and poor immune cell infiltration.[64,65] To overcome these challenges, Chen et al developed chitosan (CS)-antibody nanocomplexes by conjugating an anti-PD-L1 antibody to CS polymer, facilitating efficient transmembrane delivery.[66] Notably, the CS polymer itself induced mitochondrial damage and mtDNA release, which activated the cGAS-STING pathway. These CS-antibody nanocomplexes exhibited immunoadjuvant effects and elicited robust antitumor immune responses.[67]

Collectively, activation of cGAS-STING to upregulate innate immunity has become an attractive strategy in cancer immunotherapy.[68] Cai et al developed a novel approach using bovine serum albumin (BSA) coated zinc sulfide nanoclusters (BSA@ZnS) to enhance the efficacy of tumor immunotherapy. This nanocluster released Zn^{2+} in the tumor microenvironment (TME), activating the STING pathway and promoting the generation of ROS, which results in tumor cell death. Additionally, ROS-induced mitochondrial damage triggered the release of mtDNA, leading to further

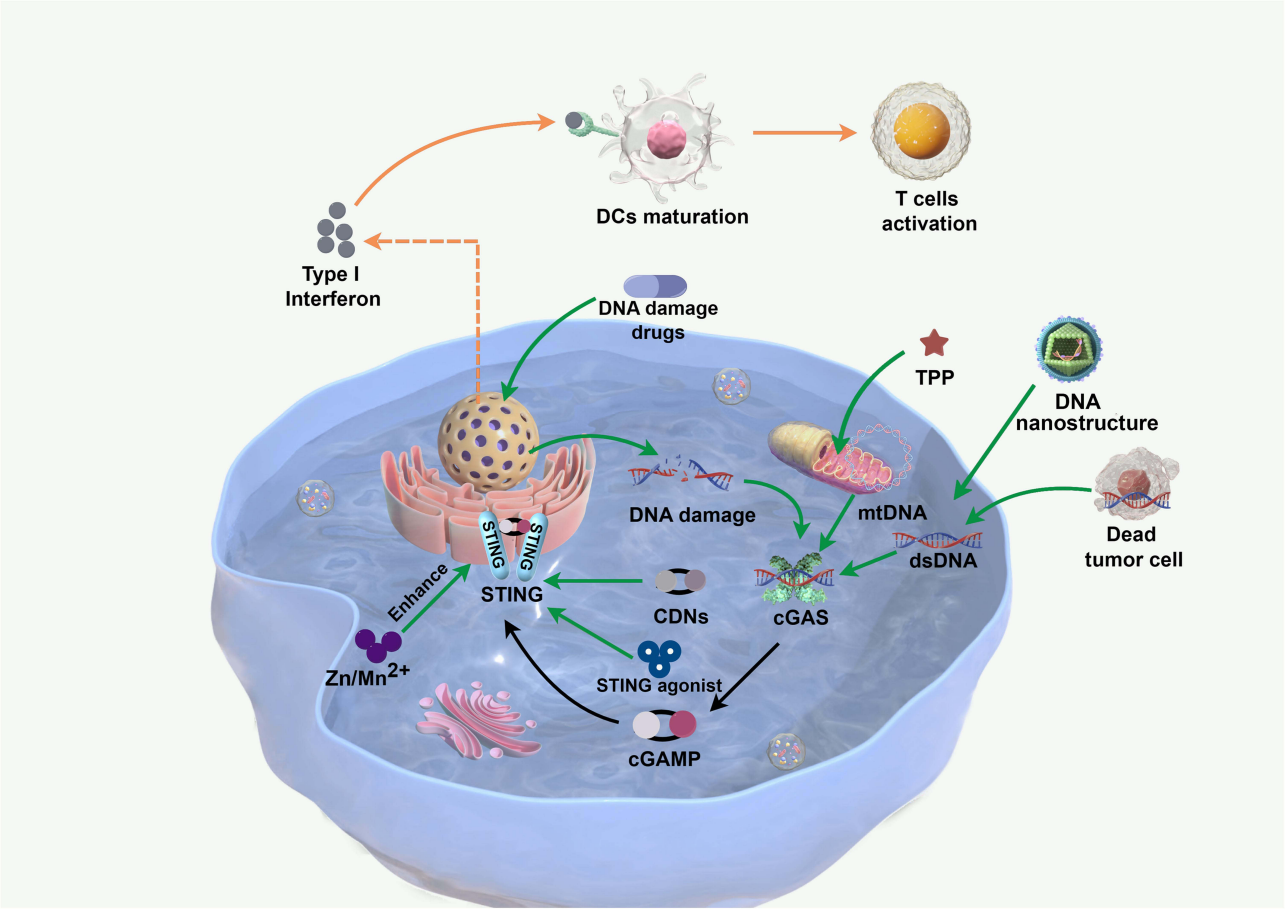

Figure 3 STING activators (including metal ions, STING agonists, endogenous DNA, and exogenous DNA) trigger innate immune responses via the cGAS-STING pathway.
Abbreviations: DCs, dendritic cells; TPP, triphenyl phosphonium; CDNs, cyclic dinucleotides; cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase.

activation of the cGAS-STING pathway.[69] H_2S produced by BSA@ZnS nanoclusters inhibited catalase activity in tumors, facilitating the infiltration of $CD8^+$ T cells and enhancing the therapeutic effect.

STING Agonists

CDNs, which are the most common STING agonists, have demonstrated potential for enhancing anticancer activity through activation of the innate immune system. cGAMP, a negatively charged CDN, is produced by cGAS in response to cytosolic dsDNA, thereby inducing IFN-I production upon STING activation.[70–74] Consequently, many cGAMP analogues have been employed as STING agonists in immunotherapy.[71,75–80] However, the delivery of cGAMP-like compounds to APCs faces several challenges. First, the negatively charged nature of cGAMP hinders its uptake by cells. Second, cGAMP is chemically unstable and easily degraded by enzymes in the bloodstream. To overcome these issues, appropriate carriers have been designed for the targeted delivery of cGAMP, and chemical modifications have been implemented to enhance its enzyme stability.[21,73,81,82]

The therapeutic efficiency of CDNs is limited by inefficient targeted delivery, low cytosolic transport efficiency, and rapid clearance. Daniel Shae et al developed STING-activating nanoparticles to enhance the delivery of CDNs and amplify STING signal transduction in the TME and lymph nodes. These nanoparticles improved the therapeutic efficiency of CDNs, enhanced the anticancer activity of T cells, and showed the potential to broaden the scope of immunotherapy.[71] James Moon's group developed a concept called "metalloimmunotherapy", wherein self-assembled nanomedicine incorporating Mn^{2+} and CDNs enhanced the uptake of STING agonist by cells and strongly activated the cGAS-STING pathway. The coordination of Mn^{2+} and CDNs induced a remarkable release

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of IFN-I and converted the "cold tumor" to "hot tumor". Local intratumoral or systemic intravenous administration of the nanoparticles triggered potent antitumor immunity and achieved significant therapeutic efficacy in multiple mouse tumor models using minimal doses of STING agonists.[76] This study highlights the development of an intravenous nanocarrier for the delivery of STING agonists, offering a promising strategy for future tumor immunotherapy research.

Activation of the cGAS-STING pathway within APCs plays a crucial role in anticancer immunity. Jacques Lux et al designed STING-activating nanoparticles by electrostatically combining APC-targeting macrovesicles (MBs) with biocompatible branched cationic polymers to enhance the loading efficiency of cGAMP.[75] Once the MBs bound to APCs, cGAMP was delivered to the cytoplasm through acoustically induced pores, thereby activating the cGAS-STING pathway and the downstream pro-inflammatory pathway, and triggering antigen-specific T cells to effectively inhibit tumor growth. Efficient delivery of STING agonists to tumor sites is a major challenge in activating cGAS-STING pathway for immunotherapy. Notably, extracellular degradation of cGAMP is largely driven by ENPP1, which rapidly hydrolyzes cyclic dinucleotides and shortens systemic exposure. Due to their limited membrane penetration and susceptibility to enzymatic degradation, CDNs are primarily administered via direct injection into the tumor. This obstacle has prompted the application of nanocarriers, such as liposomes and polymers, to facilitate the targeted delivery of CDNs to tumor sites.[83,84]

A single intravenous administration of CDNs-loaded nanocarrier provided effective therapy in multiple tumor models, highlighting its potential for immunotherapy.[85] The combination of ICB therapy with cGAS-STING-activated immunotherapy evoked a robust antitumor immune response and long-term inhibition of tumor progression.[86] A nanovesicle designed to spatiotemporally control the release of STING agonists and anti-PD-L1 antibody following radiofrequency ablation holds potential for enhancing overall therapeutic efficacy.[87] Despite these advances, complicated synthetic processes, poor stability, high required doses, and insufficient immune response have severely limited the application of cGAMP. As a non-nucleotide-based STING agonist, diABZIs exhibit higher efficiency and stronger biological activity than CDNs in stimulating the STING pathway. These compounds are capable of stably and strongly binding to the STING protein, leading to a more potent immune response.[17,79,88–91]

Much effort has been devoted to the development of CDNs and cGAMP, but the efficacy of these STING agonists is limited due to the rapid clearance and chemical instability. The non-nucleotide STING agonists have been explored in STING-activating systems. Effective reversal of immunosuppression in the TME is critical to improving the immunotherapy efficacy. Chen et al designed an immune-nanomedicine for co-delivery of cytosine–phosphate–guanine oligodeoxynucleotides (CpG ODNs) and STING agonists (DMXAA) to enhance the therapeutic effects.[92] Importantly, DMXAA robustly activates murine STING but does not activate human STING, highlighting a species-selective limitation for clinical translation. Moreover, this nanoparticle promoted the infiltration of $CD8^+$ T lymphocytes and exhibited the ability to reprogram tumor-associated macrophages. In comparison to DMXAA, the non-nucleotide STING agonist MSA-2 exhibits superior antitumor activity and has been proven to elicit a stronger immune stimulatory response.[23,93,94] Chen et al developed an innovative approach by creating esterase-activatable prodrugs on the surface of MSA-2, which were subsequently incorporated into liposomal vesicles. This strategy enhanced the therapeutic potential of MSA-2, allowing for targeted drug delivery and increased antitumor efficacy.[95] Jiang et al developed an in situ sono-activatable nanoagonist by self-assembling a sonodynamic semiconducting polymer core conjugated with MSA-2 via a singlet oxygen cleavable linker, offering a promising strategy for targeted delivery of agonists.[96] This nanoagonist not only triggered robust immunogenic cell death (ICD) but also released STING agonists in the tumor region. These findings represent significant advancements in the development of STING agonists for targeted immunotherapy, with potential implications for improving cancer immunotherapy outcomes.

With the expanding understanding of the STING pathway in immunology, numerous natural and synthetic STING agonists have been identified or developed. These compounds have been evaluated in preclinical models and clinical trials for their potential in immunotherapy, particularly for treating tumors and infectious diseases (Table 2). Currently, most STING agonists remain in the preclinical or early clinical stages of development, and formal combination therapies involving STING agonists have yet to achieve widespread clinical adoption.

Table 2 Recent STING Agonists in Clinical Trials

Name	NCT	Cancer Type	Phase	NCT Trial Status
ADU-S100	NCT03937141	Metastatic head and neck squamous cell carcinoma	II	Terminated
MK-1454	NCT04220866	Recurrent Head and Neck Squamous Cell Carcinoma	II	Completed
SB11285	NCT04096638	Advanced Solid Tumors	I	Completed
GSK3745417	NCT03843359	Advanced Solid Tumors	I	Active, not recruiting
E7766	NCT04144140	Advanced Solid Tumors or Lymphomas	I	Terminated
TAK-676	NCT04879849	Advanced Solid Tumors	I	Completed
SNX281	NCT04609579	Advanced Solid Tumors and Lymphoma	I	Terminated
BMS-986301	NCT03956680	Advanced Solid Cancers	I	Completed
XMT-2056	NCT05514717	Advanced Solid Tumors	I	Recruiting

Note: The designs of clinical trials with a NCT number could be identified in https://clinicaltrials.gov.

Endogenous DNA

Endogenous DNA, including nuclear DNA (nDNA) and mtDNA, can activate the cGAS-STING pathway when aberrantly released into the cytoplasm. Various therapeutic strategies exploit this mechanism by inducing DNA damage or mitochondrial stress to promote cytosolic DNA accumulation and enhance antitumor immune responses.

Nuclear DNA

Unlike direct STING agonist delivery (eg, cGAMP), certain small molecules can induce DNA damage and lead to the release of cytosolic dsDNA fragments, subsequently activating the cGAS-STING pathway.[97–100] Among such small molecules, doxorubicin (Dox), a classical chemotherapeutic agent, intercalates DNA, induces DNA damage in tumor cells, and promotes cytosolic dsDNA release that activates STING.[101,102] To leverage this mechanism, a novel manganese-based natural immune nanoactivator was developed to deliver Dox. The nanoactivator consisted of amorphous porous manganese phosphate that was pH-sensitive in the TME and was coated with phospholipids for tumor targeting. Upon Dox release, Dox-induced DNA damage occurred in tumor cells, producing cytosolic dsDNA and activating the cGAS-STING pathway. Meanwhile, intracellular Mn^{2+} potentiates cGAS-STING signaling, rather than acting as a direct STING agonist. The nanocarriers demonstrated excellent tumor targeting ability, promoted dendritic cell maturation, and increased cytotoxic T lymphocytes (CTLs) infiltration as well as NK cells recruitment to tumors.[103]

Platinum drugs (Pt) are well-known for their ability to form Pt-DNA complexes, leading to the obstruction of DNA synthesis and induction of DNA damage.[104–107] Expanding on this mechanism, two different Pt complexes were designed as photo-activators to trigger the cGAS-STING pathway. Upon exposure to 425 nm laser irradiation, these complexes selectively damaged mitochondrial and nuclear DNA, effectively activating the STING pathway. This activation ultimately led to cell pyroptosis and initiated an antitumor immune response. The activation of the STING pathway crucially depended on the presence of dsDNA in the cytoplasm.[108] To exploit this requirement, Chen et al developed a polymer-SN38 (7-ethyl-10-hydroxycamptothecin) conjugate capable of self-assembling into nanoparticles in vivo. These nanoparticles induced DNA damage within tumor cells and were subsequently transported to bone marrow-derived DCs via exosomes containing DNA, which resulted in the activation of the STING pathway.[109] This innovative application of SN38 nanoparticles provides a promising strategy for activating the cGAS-STING pathway in immunotherapy.[110] Moreover, chemotherapeutic drugs such as camptothecin (CPT) and cisplatin (Pt(IV)) are known to induce DNA damage, effectively activating the cGAS-STING pathway and triggering an antitumor immune response. To further enhance the synergistic effects of chemotherapy and immunotherapy, a nanoparticle was developed by assembling a ROS-responsive polymer with mPEG2k-DSPE. These nanoparticles exhibited tumor-specific accumulation and could release a hybrid platinum prodrug (CPT-Pt(IV)).[111] The efferocytosis of dying tumor cells promoted the release of dsDNA, which could in turn trigger the cGAS-STING pathway. Chen et al described a nanoparticle capable of damaging nuclear DNA and mtDNA.[112] The released dsDNA efficiently activated the STING pathway and induced M1 polarization of tumor-associated macrophages (TAM).

mtDNA

In addition to nuclear dsDNA, mtDNA leakage can activate the cGAS-STING pathway.[113–117] Raddeanin A has been shown to induce the release of mtDNA, resulting in the activation of STING and subsequent secretion of IFN-I.[118] Lei et al constructed a triphenyl phosphonium (TPP)-functionalized metal organic framework nanosheet that could target mitochondria and activate the cGAS-STING pathway.[119] This nanostimulator facilitated the ROS generation and mtDNA leakage under ultrasound, resulting in the activation of the cGAS-STING pathway. Wang et al designed a mitochondria-targeting fenofibric acid (Mito-FFa) inducer to increase mitochondrial ROS, leading to mtDNA release that subsequently facilitated cGAS-STING-dependent IFN-I secretion.[120] Overall, leveraging the DNA damage-inducing ability of small molecule chemotherapeutic drugs with nanocarriers and nanostimulators provides a promising approach for enhancing the cGAS-STING pathway and improving the outcomes of immunotherapy.

Exogenous DNA

Exogenous DNA refers to DNA originating outside the organism, typically introduced into cells or organisms through experimental methods. Both endogenous and exogenous dsDNA are recognized by cGAS and converted into cGAMP, subsequently activating the STING pathway (Table 3).

dsDNA

Delivering dsDNA to tumor cells can serve as an effective strategy to activate the cGAS-STING pathway for tumor therapy.[121,125,126] Compared to CDNs, dsDNA is relatively easy to synthesize in vitro and exhibits increased resistance to hydrolysis. Wei et al developed a 59-bp dsDNA modified on gold nanoparticles (Au-dsDNA) as a STING activator. This Au-dsDNA was then assembled with Dox and Mn_3O_4 nanoflowers to create synergistic therapy that combines immune activation and chemotherapy.[122] Using DNA nanotechnology, dsDNA was successfully modified on the surface of gold nanoparticles. The resulting nanoparticles effectively activated cGAS-STING-mediated immunotherapy, demonstrating significant antitumor effects when combined with chemotherapy drugs. Furthermore, this approach demonstrated promising performance in treating distant tumors. In another study, Wu et al designed tetrahedral DNA nanostructures adsorbed onto MnO_2 nanosheets to promote STING activation and macrophage M1 polarization, thereby enhancing tumor immunotherapy.[123]

Table 3 Strategies to Activate the cGAS-STING Pathway for Tumor Immunotherapy

STING	Activators	Tumor Model	Combined Therapy	Model Nature	Refs
Metal ions	Mn^{2+}	4T1 breast	Anti-PD-1 antibody	In vivo (intravenous injection)	[56]
	Zn^{2+}	4T1 breast	Dox and ultrasound	In vivo (intravenous injection)	[68]
		Carcinoma	H_2S gas	In vivo (intravenous injection)	[69]
	Co^{2+}	4T1 breast	Ultrasound	In vivo (intratumoral, injection)	[119]
	cGAMP	E0771 and 4T1 breast	Anti-CD11b, ultrasound	In vivo (intratumoral, injection)	[75]
		LLC tumor	AKT 1/2 inhibitor	In vivo (intravenous injection)	[76]
		Panc02	Anti-PD-L1 antibody	In vivo (intravenous injection)	[89]
	CDNs	4T1 breast and MC38	CDN-PEG-lipids	In vivo (intratumoral, injection)	[85]
	DMXAA	Hepatocellular	CpG ODNs,	In vivo (intravenous injection)	[92]
	MSA-2	4T1 breast	Ultrasound	In vivo (intravenous injection)	[93]
Endogenous DNA	nDNA	4T1 breast	SN38	In vivo (intravenous injection)	[100]
		Biu87 and Mb49 tumor	Pt(IV), PD-L1	In vivo (intravenous injection)	[105]
		Hela tumor	Pt(II), PDT	In vivo (intratumoral, injection)	[108]
		MFC tumor	Pt(IV), PD-L1	In vivo (intravenous injection)	[112]
	mtDNA	4T1 tumor	Mn^{2+}, CRISPR/Cas9	In vivo (intravenous injection)	[113]
		4T1 breast	Mn^{2+}, PDT, H_2S	In vivo (intravenous injection)	[114]
Exogenous DNA	dsDNA	CT26 tumor	Anti-PD-1	In vivo (intratumoral, injection)	[121]
		B16F10 tumor	Dox, Mn^{2+}	In vivo (intravenous injection)	[122]
	DNA NPs	Hepa1-6 tumor	Mn^{2+}	In vivo (intratumoral, injection)	[123]
	DNAzyme	4T1 breast	RGD, Mn^{2+}	In vivo (intravenous injection)	[124]

DNA Nanostructures

Tetrahedral DNA nanostructures can activate the STING pathway. Moreover, the release of Mn^{2+} further enhanced the expression of IFN-I, thus eliciting a potent antitumor response in vivo. This innovative approach utilizing DNA nanotechnology demonstrates its potential for enhancing tumor immunotherapy through STING pathway activation and macrophage modulation. Zhang et al creatively designed a tetrahedral DNA nanostructure (TDN), which was formed by complementary base pairing between interferon-stimulating DNA (ISD) chain and three specific single-stranded DNA sequences.[127] The platinum (II) chemotherapeutic complex 56MESS was incorporated into the double-stranded DNA of tetrahedral DNA nanostructure. Importantly, ISD-modified TDN (TDN^{ISD}) efficiently activates the STING pathway and elicits robust antitumor immune responses. Moreover, the incorporation of 56MESS into TDNISD further enhanced its ability to activate the cGAS-STING pathway. This innovative approach showcases the potential of DNA as a versatile building block for constructing intricate nanoarchitectures.

DNAzymes

Deoxyribozymes (DNAzymes) are catalytic single-stranded DNA fragments with RNA-cleavage activity.[128–130] Viruses are highly immunogenic and can activate the dsDNA-dependent cGAS-STING pathway by presenting viral antigens to the immune system. Virus-based immunotherapy has displayed potential in tumor treatment. However, viruses are associated with significant adverse effects and uncontrollable insertion of genetic material into the host genome, which limits their application. Herpesviruses, as a major human pathogen, can trigger mtDNA during infection, causing mtDNA to escape into the cytoplasm and eventually activate innate immunity. DNAzymes that specifically cleave TFAM mRNA reduce TFAM expression and induce mtDNA release, mimicking effects seen in herpesvirus infection. DNAzymes were loaded into manganese-doped ZIF-90 nanoparticles (Mn-ZIF-90) and then encapsulated within erythrocyte membranes.[124] The DNAzymes-loaded Mn-ZIF-90 nanoparticles, resembling virus-like particles, entered organelles and cytoplasm, similar to herpesviruses, resulting in downregulated expression of TFAM-related proteins and the release of mtDNA. This activation of the cGAS-STING pathway stimulated the secretion of IFN-I, leading to the elimination of primary tumors and prolonging median survival. This innovative approach, based on DNAzymes-loaded Mn-ZIF-90 nanoparticles and erythrocyte membranes, exploits the potential of DNAzymes as an alternative to traditional virus-based immunotherapy. It avoids off-target effects and uncontrollable insertion of genetic material caused by virus-based therapy and opens promising paths for the future of cancer therapy.

In conclusion, the activation of the cGAS-STING pathway can be achieved through diverse classes of activators, each with distinct advantages and limitations. (1) Metal ions enhance cGAS-DNA binding affinity and act as cost-effective immune adjuvants, but suffer from nonspecific PRR activation and neurotoxicity risks; (2) Synthetic STING agonists offer high target specificity and combinatory potential, including low bioavailability (<15%) for charged CDNs and haplotype-dependent response variability. (3) Endogenous DNA (eg, mtDNA, nDNA) leverages pathological relevance and biocompatibility, but exhibits concentration-dependent duality—low doses promote immunity while high doses induce T cell exhaustion. (4) Exogenous DNA provides potent IFN-I induction and vaccine synergy, yet risks immunopathology. Collectively, while metal ions and endogenous DNA offer advantages in cost-effectiveness and relative safety, synthetic agonists offer precision, and exogenous DNA enables strong immunogenicity.

Combination with Antitumor Modalities

ROS-based antitumor therapies induce DNA damage and reprogram the TME, resulting in enhanced activation of the cGAS-STING pathway. The combination of ROS-based therapies with STING pathway activators holds promise as a therapeutic strategy in tumor immunotherapy.[131,132] Non-ROS-based therapies induce cytosolic DNA release, improve tumor immunogenicity, and directly modulate immune-related genes, thereby activating and amplifying the cGAS-STING pathway (Figure 4). ROS-based therapies and non-ROS-based therapies have garnered significant attention as complementary approaches to cGAS-STING-activated immunotherapy.[133–135] Integrating these modalities with cGAS-STING pathway activation has the potential to significantly enhance overall therapeutic efficacy (Table 4).

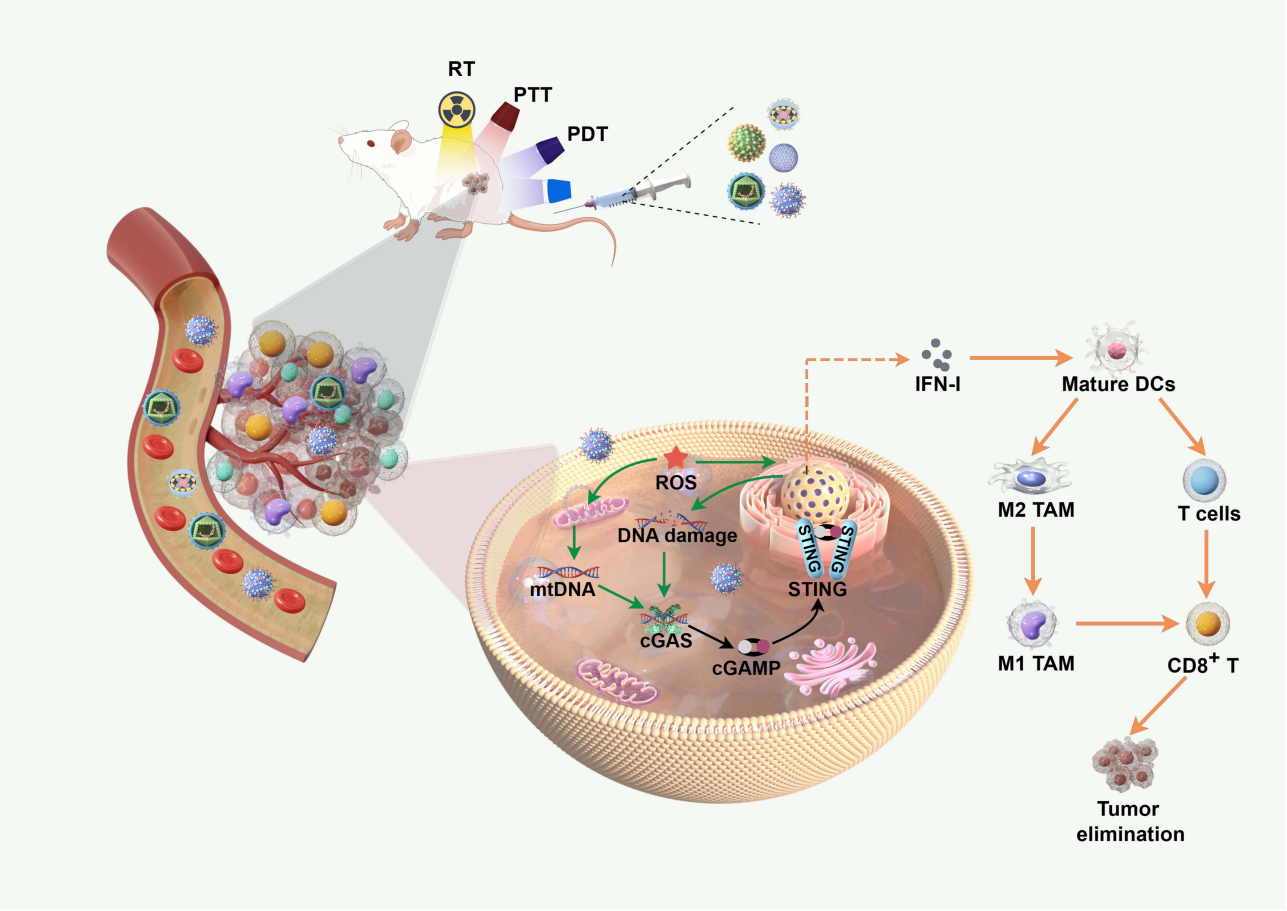

Figure 4 Illustration of synergistic combinations of cGAS-STING-mediated immunotherapy with other therapeutic modalities, including PTT, PDT, SDT, and RT.
Abbreviations: RT, radiotherapy; PTT, photothermal therapy; PDT, photodynamic therapy; SDT, sonodynamic therapy; TAM, tumor-associated macrophages; IFN-I, type I interferon.

ROS-Based Antitumor Therapies

Photodynamic Therapy

Photodynamic therapy (PDT) utilizes photosensitizers irradiated at specific wavelengths to convert molecular oxygen into ROS, which exhibit potent antitumor effects.[132,143,144] Moreover, the generated ROS can cause mitochondrial damage and the release of mtDNA, subsequently activating the cGAS-STING pathway. Combining PDT with cGAS-STING activation has the potential to enhance the efficacy of antitumor immunotherapy, similar to chemodynamic therapy (CDT).[145–149] DCs play a pivotal role in initiating immune responses through ICD and cross-presentation of antigens.[133] To further advance this approach, Luan et al developed a nanoparticle capable of modulating multiple steps

Table 4 Combination Strategies for cGAS-STING Activation in Tumor Therapy

Combination Modalities	Specific Therapy	Carrier	Link to STING-Based Immunotherapy	Refs
ROS-based therapy	PDT	CC-6td	Increased $^1O_2$ ICD	[83]
	SDT	BSA@ MnO_2	Increased ROS production, ICD	[136]
	Radiotherapy	Nd@NaLuF4@PEG	Mn^{2+}, Increased ROS production	[137]
	CDT	UCNPs@$mSiO_2$	Induced ROS induction	[138]
Non-ROS-based therapy	PTT	EV@RGT	Increased ROS induction	[139]
	CRISPR/Cas systems	$HMnO_2$	Knockdown the PD-L1 immune checkpoint	[140]
	CAR-T	CAR-T	Induced IL-18 secretion,	[141]
	Virus-based therapy	Coxsackievirus B5	Increased damaged DNA	[142]

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of the immune response by co-assembling photosensitized chlorin e6 (Ce6), celecoxib, and 6-thio-2′-deoxyguanosine (6-thio-dG).[83] Under 660 nm laser irradiation, Ce6 induced an ICD effect. 6-thio-dG, a DNA synthesis inhibitor, caused DNA damage in tumor cells, leading to the generation of cytosolic dsDNA that activated the cGAS-STING pathway and promoted IFN-I secretion. Together, these effects augmented antitumor immunity. This nanomedical approach holds potential for tumor-targeted immunotherapy by modulating multiple steps of the DC-initiated immune response, thereby suppressing tumor growth and reducing postoperative recurrence risk. The co-assembled nanoparticles, featuring Ce6, celecoxib, and 6-thio-dG, represent a promising strategy for enhancing the therapeutic outcomes of PDT and cGAS-STING pathway-mediated immunotherapy in the field of cancer treatment. PDT generates potent antitumor effects, while activation of the cGAS-STING pathway can provoke a long-lasting antitumor immune response. The amphiphilic phenolic polymer (PF) was conjugated with Ce6 for mitochondria-targeted PDT, leading to excessive mtDNA damage. Released Mn^{2+} together with tumor-derived mtDNA synergistically activated the cGAS-STING pathway and promoted STING-dependent immunity.[150] In addition to photosensitized Ce6, polymeric metal-organic framework (PMOF) nanoparticles, comprising meso-tetra(carboxyphenyl)porphyrin (TCPP) and the STING agonist SR-717, were developed for photodynamic-immunotherapy. The synergistic action of photodynamic therapy (PDT) and SR-717 amplified anti-tumor immunity and reversed the suppressive tumor microenvironment, effectively inhibiting the growth of both primary and distant tumors.[151]

Sonodynamic Therapy

Sonodynamic therapy (SDT) is a promising approach that utilizes ultrasound (US) to induce the generation of ROS in tumors.[68,93,119,136] However, the complex and heterogeneous TME often impairs ROS-based cytotoxicity by reducing the oxidative stress in cancer cells.[152,153] To address this issue, a novel nanoparticle-based sensitization strategy has been developed using ultrasmall oxygen-deficient MoOX nanoparticles (NPs) for US-enhanced cancer metalloimmunotherapy. These MoOX NPs generated substantial ROS and effectively induced ICD and cancer cell damage.[152] Moreover, MoOX NPs stimulated DC maturation and activated the cGAS-STING pathway, thereby enhancing the immunotherapy effect. This innovative approach of incorporating MoOX NPs as nanosensitizers in US-enhanced tumor metalloimmunotherapy represents an encouraging strategy that can overcome the protective mechanisms of the tumor microenvironment. By effectively increasing the ROS levels, MoOX NPs can enhance the cytotoxic effects of SDT in cancer cells. This holistic strategy substantially improves the therapeutic outcomes of SDT in cancer treatment. An MSA-2-coloaded Wurster-type covalent organic framework was developed as an immune activator. Under sono-irradiation, this nanoactivator produced ROS to induce Gasdermin-D-mediated pro-inflammatory pyroptosis and trigger STING-related innate immunity.[154]

Radiotherapy

Radiotherapy (RT) is an effective treatment modality that utilizes radiation to kill cancer cells and achieve therapeutic outcomes.[155,156] One mechanism by which RT exerts antitumor effects is the generation of ROS, which induces DNA damage. This DNA damage leads to the release of dsDNA from the nucleus, subsequently activating the cGAS-STING pathway.[134,137,157–160] Dai et al developed nanocomposites by assembling metal polyphenol networks and radiosensitizers under the coordination of Mn^{2+} ions.[137] Upon internalization of these nanocarriers, the radiosensitizers sensitized cancer cells to X-ray radiation, while Mn^{2+} ions promoted the activation of the STING pathway, resulting in the release of IFN-I and enhanced antitumor immunotherapy. These radiosensitized and STING-activated nanocarriers exhibited the ability to promote DC maturation, suppress primary tumor growth, and induce systemic antitumor immunity against metastases. The combination of RT and immunotherapy demonstrated a synergistic inhibition of tumor growth. Deng et al constructed RT-induced nanoparticles ($\alpha PDL1@MnO_2$) for the combination of RT and ICB therapy.[161] This nanomedicine effectively overcame radiation resistance and reversed the immunosuppressive TME, promoting the infiltration of $CD8^+$ T lymphocytes. Furthermore, released Mn^{2+} significantly enhanced the sensitivity of the cGAS-STING pathway and IFN-I secretion. Such a strategy efficiently inhibited the growth of primary tumors and triggered a strong abscopal effect to inhibit tumor metastases.

In another study, STING agonists were encapsulated in tannic acid nanocarriers using metal coordination with Mn^{2+} to form a metal-polyphenol network.[162] Locally administered, these carriers alleviated tumor hypoxia and generated ROS

upon X-ray irradiation. The release of DNA fragments following apoptosis facilitated the production of CDNs, thereby significantly enhancing cGAS-STING pathway-mediated tumor immunotherapy. Furthermore, this approach effectively promoted DCs maturation and activated cytotoxic immune cells, resulting in the inhibition of tumor growth. The combination of RT and immunotherapy holds great promise for cancer treatment. The utilization of nanocomposites and nanocarriers that sensitize cancer cells to radiation and activate the cGAS-STING pathway improves the therapeutic outcomes of radiotherapy by enhancing immune responses. With their ability to promote DC maturation, inhibit tumor growth, and elicit systemic immunotherapeutic effects, these innovative approaches provide new avenues for advancing cancer therapeutics. A novel lipid-modified manganese diselenide nanoparticle ($MnSe_2$-lipid) was developed to overcome radioresistance and activate the cGAS-STING pathway.[163] This $MnSe_2$-lipid increased radiosensitivity and provided radioprotection in esophageal squamous cell carcinoma (ESCC). High-Z Hf_6 secondary building units (SBUs) could enhance the therapeutic effect of X-ray radiation. A bifunctional MSA-2 conjugated MOF plus low-dose X-ray irradiation elicited sustained STING activation and promoted the infiltration of immune cells.[164] Chen et al designed the FeMn-NC_e dual-atom nanozymes for augmented radiodynamic immunotherapy.[165] These nanozymes activated the cGAS-STING pathway and induced long-term antitumor immunity, effectively inhibiting tumor growth and metastasis following a single low-dose X-ray treatment.

Chemodynamic Therapy

Mn^{2+} plays a vital role in the CDT-enhanced cGAS-STING pathway for tumor therapy.[166–168] Zhang et al developed a membrane-coated cascade nanozyme (gCM@MnAu) for cancer therapy, resulting in potentiated CDT-induced ICD. These nanozymes showed excellent catalase-like activity and activated the STING pathway by releasing Mn^{2+}, thereby eliciting antitumor responses.[169] 4T1 cancer cell membrane-modified hydrogenated manganese oxide nanoparticles (mHMnO-Dox) were designed to induce ROS-mediated CDT by Fenton-type reaction.[170] The released Mn^{2+} generated ROS and activated the cGAS-STING pathway to boost DC maturation and the antitumor immune response. Yang et al designed a PEGylated, metal-coordinated nanotheranostic (MGP) incorporating the nucleoside metabolic inhibitor gemcitabine (Gem). MGP caused DNA damage and activated the cGAS–STING pathway; Mn^{2+}-mediated CDT synergistically amplified STING activation and induced IFN-I production. These nanotheranostics induced ICD and elicited robust antitumor responses.[166]

Non-ROS-Based Antitumor Therapies

Photothermal Therapy

Photothermal therapy (PTT) is a promising approach in which photothermal agents convert absorbed light into heat upon irradiation at specific wavelengths, leading to localized tumor cell destruction.[138,171,172] Activation of the cGAS-STING pathway has emerged as a powerful strategy in tumor immunotherapy. Combining PTT with STING pathway-mediated immunotherapy can synergistically enhance antitumor activity.[79,139,173–176] Wang et al assembled an amphiphilic polymer, the photothermal agent IR780, and Mn–Zn sulfide nanoparticles into polymeric micelles.[177] Under near-infrared light (NIR) irradiation, the micelles released Mn-Zn sulfide nanoparticles, which liberated Mn^{2+}. Released Mn^{2+} enabled CDT by promoting ROS generation, increasing ICD, and exposing damage-associated molecular patterns (DAMPs). IR780 preferentially accumulated at the tumor site, allowing efficient photothermal ablation and further amplifying CDT. Concurrently, Mn^{2+} activated the cGAS-STING pathway, inducing IFN-I production and enhancing antitumor immunity. Zuo et al established a micro-scale cytotoxic T-cell-inspired oncolytic system to improve the immune response of anti-PD -1 therapy and STING activation by NIR irradiation.[178] Similarly, a membrane-bionic nanoparticle was developed to amplify glioblastoma immunotherapy. This innovative platform synergizes photothermal PTT with PD-1 inhibitors, thereby activating the cGAS-STING pathway, triggering the ICD effect, and eliciting a potent antitumor immune response.[179] A mesoporous nanozyme with POD-like and CAT-like activities could alleviate tumor hypoxia and thereby restore cGAS-STING signaling.[180]

Mild-temperature PTT has achieved notable success in precisely inducing tumor inflammatory responses and modulating the TME.[181] The therapeutic efficacy of small-molecule STING agonists is often limited due to insufficient accumulation, short duration of drug efficacy, and rapid clearance in the TME. Therefore, a versatile photoactivatable

nanoparticle was designed to enhance the sustained release and intratumoral retention of the STING agonist diABZIs.[79] This multifunctional nanoparticle successfully activated the cGAS–STING pathway and achieved sustained antitumor immune responses.

Immune Checkpoint Blockade

ICB therapy has been widely used in cancer immunotherapy, but it often fails to elicit robust and durable immune responses.[182–184] A nanovaccine composed of cGAMP and monophosphorylated lipid A (MPLA) was designed to enhance ICB therapy. The combination of STING and TLR4 agonists elicited long-term antitumor immunity and increased responsiveness to anti-PD-1 therapy.[185] Xiao et al developed a pH and enzyme dual-responsive nanomedicine for programmed antitumor immunity.[90] This nanomedicine specifically targeted the lymphatic system to activate DCs and T cells, inducing robust ICD and triggering tumor cell proptosis. Liposome nanoparticles (Lipo-NPs) were designed to promote the infiltration of tumor-infiltrating lymphocytes (TILs).[186] cGAMP, together with Zn^{2+}, was selected in combination with ICB therapy, inhibiting melanoma growth and activating memory T cells. A novel pocket-independent STING-activating agonist (piSTINGs) was fabricated to strengthen the STING-related immunotherapy.[187] The combination of piSTING-adjuvanted vaccine with aPD-1 therapy enhanced the effectiveness of ICB. Overall, synergistic integration of ICB with cGAS-STING activation elicits potent antitumor immunity.[188]

CRISPR/Cas Systems

CRISPR/Cas-assisted immunotherapy has attracted significant attention in cancer treatment. A novel nanosystem was engineered by integrating tumor-microenvironment-biodegradable H-MnO_2 with liposomes loaded with CRISPR/Cas9 components.[189] This CRISPR/Cas nanosystem enabled precise editing of protein tyrosine phosphatase N2 (PTPN2), subsequently stimulating the cGAS-STING pathway, boosting innate antitumor immunity while reshaping the immunosuppressive TME. Lu et al developed a CRISPR-Cas9/sgPD-L1 nanosystem to activate the cGAS-STING pathway in combination with ICB therapy.[140] In their design, the CRISPR-Cas9 plasmid and the STING agonist MSA-2 were loaded onto hollow manganese dioxide (HMn) nanoparticles to knock down PD-L1 expression and activate the cGAS-STING pathway. This approach effectively inhibited tumor growth and induced durable antitumor immunity.

CAR-T

The role of intrinsic cGAS-STING activation in T cells remains incompletely understood; peripheral blood $CD8^+$ T cells from cancer patients have shown markedly reduced expression of components of the cGAS-STING cascade.[141] In adoptively transferred $CD8^+$ T cells, the cGAS-STING pathway is crucial for antitumor responses, aiding the maintenance and differentiation of stem-cell-like $CD8^+$ T cells by regulating TCF1 expression and restraining Akt activity. A STING agonist enhanced the formation of stem-like central memory $CD8^+$ T cells and improved the efficacy of chimeric antigen receptor (CAR) T cell therapy in a xenograft model, highlighting its potential to improve CAR-T cell-based cancer therapies.[190] Electroporation-induced toxicity in primary human T cells was mediated by the cytosolic cGAS-STING pathway and could be mitigated by using an isotonic buffer. This optimized buffer reduced cGAS–STING surveillance, enabling the production of CAR-T cells with up to 20-fold higher yields and greater antitumor activity than those produced by standard electroporation or lentiviral transduction methods.[191] The buffer improved the efficiency of DNA transfection in primary T cells and human hematopoietic stem cells, suggesting a potential for optimizing electroporation-mediated DNA delivery for genome-engineered T cell production.[192,193]

Virus-Based Therapy

Recently, virus-based carriers have been applied to cancer therapy.[194,195] A microscale cytotoxic T-cell-inspired oncolytic system (TIO) was developed to lyse cancer cells under 980 nm NIR irradiation.[178] The inflammation triggered by oncolysis was crucial to oncolysis-based antitumor immunity. These TIOs improved the responses to anti-PD-1 therapy and cGAS-STING activation. The synergistic effect of oncolysis and STING activation could provide robust antitumor immunity and elicit immune memory. Coxsackievirus B5/Faulkner (CV-B5/F) showed potential as an oncolytic virus for non-small cell lung cancer (NSCLC).[142] CV-B5/F induced apoptosis and autophagy in NSCLC cells, and its effectiveness was enhanced when combined with DNA-dependent protein kinase (DNA-PK) or ataxia telangiectasia mutated protein

(ATM) inhibitors. Viral infection triggers ER stress-related pro-apoptosis and autophagy signals, and inhibition of DNA repair exacerbates double-stranded DNA breaks, thereby activating the cGAS-STING pathway. The study identifies CV-B5/F combined with DNA-PK/ATM inhibitors as a potential synergistic therapy for NSCLC, with no treatment-related mortality observed.

Antiviral Defense

SARS-CoV-2

Fan et al reported an effective mRNA nanovaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[196] Mn^{2+}, which served as a STING activator, was encapsulated in a newly synthesized ionizable lipid (IC8). IC8/Mn@D lipid nanoparticles exhibited robust immunogenicity and good safety. Zhou et al reported that SARS-CoV-2 activates innate immunity via the cGAS-STING pathway.[197] Targeting the cytoplasmic chromatin-cGAS-STING axis may enhance host defense against viral infections. Zhang et al engineered STING agonist-armed lipid nanoparticles (SAL12-LNPs) that co-deliver SARS-CoV-2 Spike mRNA and a non-nucleotide STING agonist for synergistic antiviral immunization in murine models.[198] The nanovaccine encoded the Spike glycoprotein and concurrently engaged the cGAS-STING pathway. Liu et al developed STING pathway-activating complexes (SPAC) against SARS-CoV-2.[199] In infectious models, including cytomegalovirus (CMV) and SARS-CoV -2, this universal STING mimic provided broad-spectrum antiviral protection. Adeno-associated viruses (AAVs) have also emerged as promising vaccine vectors. A novel Pickering emulsion platform enhanced AAV vaccine efficacy by improving in vivo distribution, diversifying endocytic pathways, and boosting APC transduction efficiency.[200] Additionally, it activated the cGAS-STING pathway, strengthened immune responses, reduced liver accumulation, and increased vaccine safety and cross-protective potential.[201]

Influenza Viruses

STING agonists have emerged as a promising strategy for combating influenza viruses.[202] By activating innate immune pathways, they enhance antigen presentation and promote durable T-cell responses, making them ideal for next-generation vaccine development. For instance, single-component, self-assembling protein nanoparticles (SApNPs) composed of the matrix protein 2 (M2e) were engineered as a pan-influenza A vaccine.[34] STING agonists were loaded onto the SApNPs to induce robust and durable T cell responses. Tsai et al developed potent M2e-loaded polymeric nanoshells co-encapsulating high densities of M2e peptides and STING agonists, achieving robust and long-term protection against heterotypic influenza viruses after a single dose.[35] Sheng et al developed a hybrid influenza nanovaccine (THM-HA@Mn) incorporating a STING agonist to enhance immune activation, antigen presentation, and sustained response, offering a potent and safe VLP-based vaccine strategy.[203] Leekha et al designed a nanoSTING platform that served as a broad-spectrum immune activator against respiratory viral infections.[204] A single intranasal dose protected against SARS-CoV-2 variants and influenza strains, including oseltamivir-resistant viruses, by activating both interferon-dependent and interferon-independent pathways. These findings highlighted NanoSTING's potential as an effective and safe therapy for respiratory virus control. Gallovic et al introduced a scalable microparticle-based vaccine adjuvant incorporating the STING agonist cGAMP, enhancing immune responses and achieving significant dose-sparing effects.[205] In ferrets, this formulation reduced viral shedding and provided superior protection compared to seasonal influenza vaccines. Notably, a single dose conferred sustained protection against lethal influenza infection for up to a year, highlighting its potential for durable respiratory virus vaccines. Hendy et al designed a polymeric cGAMP microparticle with broad-spectrum activity against influenza viruses.[206] Together, these advancements highlight STING agonists as a key component in next-generation influenza vaccines, offering broad, durable, and effective protection against respiratory viruses.

Others

A novel nanovaccine was developed to deliver subunit viral antigens and STING agonists in a virus-like manner.[207] The STING agonists were encapsulated within capsid-like hollow polymeric nanoparticles, which exhibited pH-responsive release, significant local immune activation, and reduced systemic reactogenicity.[9] In mice immunized with the Middle

East respiratory syndrome coronavirus (MERS-CoV) nanoparticle vaccine candidate, potent neutralizing antibodies and antigen-specific T cell responses were elicited, supporting the efficacy of the nanoparticle vaccine. A manganese-based metal-phenolic network (MPN) hydrogel vaccine (CGMR) provided strong and long-lasting humoral immunity against rabies with a single dose.[208] By acting as a "hydrogel antigen depot" and activating the cGAS-STING pathway, CGMR enhanced antigen presentation and immune responses, offering a promising strategy for rabies prevention and other infectious diseases. Wen et al reported that Epstein-Barr virus (EBV) infection induced olfactomedin 4 (OLFM4) secretion via large microvesicles (MVs) to promote tumor progression through Hippo signaling. OLFM4, regulated by the cGAS-STING pathway, bound to FAT1, disrupting its interaction with MST1 and activating YAP in recipient cells.[209] Yang et al revealed that the vaccinia virus protein C7 inhibited IRF3 activation, impairing immune responses during pulmonary infection.[210] Type II alveolar epithelial cells (AECIIs) detect the virus via MDA5 and STING pathways, triggering IFN-I production and recruiting $CCR2^{+}$ inflammatory monocytes that differentiate into Lyve1−interstitial macrophages (IMs) to control viral replication. These findings highlight the critical role of AECIIs in initiating innate immune defense against acute poxvirus infection.[211–213]

Conclusion and Outlook

The cGAS-STING pathway has become a key focus in antitumor immunotherapy and antiviral defense. While STING agonists enhance tumor immunotherapy and viral infection responses, their clinical use is hindered by high cost, poor delivery, and low efficacy. To overcome these barriers, nanoparticles and cGAMP surrogates are being developed to improve delivery and bioavailability.

Alternative activation strategies, including metal ions, endogenous DNA, and exogenous DNA, are being developed. STING activation can convert "cold" tumors into "hot" tumors, but achieving specific targeting and robust activation in vivo remains challenging. Combining STING-directed immunotherapy with other modalities offers the potential to boost antitumor efficacy. Nanovaccines delivering STING activators have also advanced antiviral applications, notably against SARS-CoV-2 and influenza.

In summary, progress in STING agonists, nanoparticle delivery systems, and alternative activators has meaningfully advanced tumor immunotherapy and antiviral strategies. Critical challenges remain, including optimizing delivery mechanisms, improving molecular stability, and refining dosing regimens. Future priorities include the following: (1) development of more potent, selective STING agonists with optimized pharmacokinetics and reduced systemic inflammatory toxicity; and (2) rational combination strategies to overcome resistance, for example, pairing cGAS-STING activation with immune checkpoint blockade (anti-PD-1/PD-L1, anti-CTLA-4), or with ROS-based therapies that increase cytosolic DNA and tumor immunogenicity. These directions are likely to broaden the clinical utility of cGAS-STING-targeted therapies and improve patient outcomes.

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Disclosure

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