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REVIEW

cGAS–STING pathway activation drives the cold-to-hot tumor transition and sensitizes immunotherapy

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ABSTRACT The cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) pathway is a central sensor of innate immunity that plays critical roles in recognizing cytosolic DNA and initiating antitumor immune responses. However, this pathway exhibits extensive spatiotemporal duality and context dependency in tumor regulation. In recent years, modulating this pathway to convert immunologically "cold" tumors into immunologically "hot," inflamed tumors has emerged as a cutting-edge strategy to reverse resistance to immune checkpoint inhibitors (ICIs). This review outlines the molecular mechanisms underlying the activation and regulation of the cGAS–STING pathway, with emphasis on its complex role in orchestrating the tumor immune phenotypic switch. A nuanced analysis of the pathway's duality distinguishes between acute immunostimulatory activation and chronic, pro-tumorigenic inflammation driven by chromosomal instability (CIN). Furthermore, current evidence regarding direct and indirect T-cell modulation, as well as pathway-mediated remodeling of the tumor microenvironment (TME) across diverse malignancies, is discussed in detail. Crucially, the current bottlenecks in clinical translation are described, including evaluation of the failure of first-generation agonists and the promise of next-generation delivery platforms such as antibody-drug conjugates (ADCs) and nanoparticle systems. Finally, a novel strategic framework is proposed involving mapping of specific STING-targeted modalities to distinct TME phenotypes, such as immune-desert, immune-excluded, and exhausted-inflamed states. A detailed understanding of the cGAS–STING axis has substantial value in providing theoretical guidance and supporting clinical translation in the development of next-generation combination immunotherapies, as well as broadening the patient population benefiting from clinical interventions.

KEYWORDS cGAS–STING pathway; tumor microenvironment; cold-to-hot tumor transition; immunotherapy; STING agonists

Introduction

In recent years, cancer immunotherapy, particularly the use of immune checkpoint inhibitors (ICIs), has transformed the treatment landscape for various advanced malignancies[1]. However, in clinical practice, only a subset of patients achieve durable clinical benefits, and the overall response rate remains to be improved[2]. A key factor contributing to this heterogeneity in treatment efficacy is the complexity of the tumor microenvironment (TME), particularly its immunological features[3]. On the basis of the presence and functional state of tumor-infiltrating lymphocytes (TILs), the TME can be conceptualized as "immune-inflamed" ("hot" tumors) or "immune-excluded"/"immune-desert" ("cold" tumors)[4-6]. "Hot" tumors are typically enriched in cytotoxic T lymphocytes (CTLs) and are sensitive to ICIs. In contrast, "cold" tumors are characterized by a paucity of T-cell infiltration, or the presence of immunosuppressive mechanisms, leading to poor or refractory responses to current immunotherapies[7]. Therefore, elucidating the intrinsic mechanisms and developing strategies to convert "cold" to "hot" tumors are central challenges in expanding the patient population benefiting from immunotherapy and enhancing therapeutic efficacy.

Innate immune signaling pathways link tumor cell stress to adaptive antitumor immune responses[8,9]. Among these pathways, the cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) pathway, a central cytosolic

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DNA-sensing mechanism, has garnered substantial attention in recent years[10]. This pathway is crucial in reshaping the tumor immune microenvironment and might theoretically provide a key driving force for the conversion of "cold" to "hot" tumors[11]. This review provides an in-depth analysis of the heterogeneity of this pathway across various malignancies and critically evaluates the duality of its characteristics. Furthermore, the primary bottlenecks in its clinical translation are highlighted, specifically the discrepancies between preclinical findings and clinical trial outcomes. Targeted solutions are additionally explored from the perspectives of administration modes and pharmacological intervention mechanisms, including non-nucleotide small molecules, sophisticated targeted delivery systems, immune-stimulating antibody conjugates (ISACs), antibody–drug conjugates (ADCs), and bioengineered platforms such as bacterial vectors and exosomes. Ultimately, by integrating these innovative delivery technologies with specific TME phenotypes, we provide a chain of translational evidence. This framework is designed to offer a theoretical foundation for rationale-driven combination therapies, as well as novel perspectives to help overcome current resistance to immunotherapy.

Molecular activation and signal transduction of the cGAS–STING pathway

The cGAS–STING pathway is a central sensor of the innate immune system. By detecting aberrant cytosolic DNA, it acts as a crucial "sentry" for maintaining cellular homeostasis. Its molecular mechanism is characterized by multilayered dynamic regulation, encompassing the entire process from DNA recognition to immune effector activation. The molecular activation process can be divided into stages, as described in the following sections.

Activation: cytosolic nucleic acid sensing and generation of the second messenger cGAMP

cGAS is a core component of the cGAS–STING pathway. This nucleotidyltransferase binds both endogenous and exogenous cytosolic double-stranded DNA (dsDNA). cGAS recognizes abnormally accumulated dsDNA in tumor cells in a sequence-independent but length-dependent manner, and subsequently activates the innate immune response[12]. The diverse sources of cytosolic DNA include primarily DNA leaked from the nucleus or mitochondria; DNA acquired from the extracellular microenvironment; and pathogenic DNA from DNA viruses, retroviruses, bacteria, or parasites[13,14]. During the DNA recognition stage, the N-terminal domain of cGAS, because of its positive charge, binds the phosphate backbone of dsDNA, whereas the C-terminal catalytic domain interacts with the DNA double helix through a zinc finger motif. This synergistic action of the two domains induces cGAS dimerization and results in the formation of a catalytically active 2:2 cGAS–DNA complex[15,16] (**Figure 1A**). Structural biology studies have further elucidated the mechanism underlying the stabilization of the conformation of this complex: each cGAS molecule forms a "head-to-head" arrangement with an adjacent molecule, thereby promoting oligomerization[17]. Simultaneously, interactions between the DNA-binding surfaces of cGAS and the DNA backbone maintain the stable conformation of the complex.

Whereas the 2:2 dimer serves as the basic catalytic unit, the geometric properties of DNA play a critical regulatory role in achieving optimal cGAS activity. Long DNA strands (>45 bp) induce the formation of ladder-like cGAS oligomers and promote the assembly of stable "DNA–protein lattices"[18], thereby increasing enzymatic activity. DNA architectural proteins, such as the bacterial DNA-binding protein HU, mitochondrial transcription factor A (TFAM), and high mobility group box 1 protein (HMGB1), bend dsDNA into U-shaped structures[17] and cooperatively facilitate cGAS polymerization. Furthermore, the human cGAS-specific residues Lys187 and Leu195 promote the sequential binding of long DNA strands by attenuating the DNA-binding affinity of the protein. Beyond these mechanisms, cGAS enzymatic activity is regulated by liquid-liquid phase separation (LLPS). When the cytosolic DNA concentration reaches a critical threshold, cGAS and dsDNA form molecular condensates through multivalent interactions. This dynamic phase transition not only protects DNA against nuclease degradation but also markedly enhances the subsequent synthesis efficiency of cyclic GMP-AMP (cGAMP) *via* spatial confinement effects[19,20].

During catalysis, the N-terminal domain of cGAS disengages from phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$] membrane anchors, thereby exposing the catalytic pocket. The enzyme subsequently uses the substrates GTP and ATP to produce a cyclic dinucleotide (CDN) with mixed phosphodiester linkages: G(2′-5′)pA(3′-5′)p, also known as 2′,3′-cGAMP or simply cGAMP (**Figure 1A**). This mammalian isomer has stronger binding affinity than bacterially derived CDNs for the STING protein[12,17].

Furthermore, the ligand spectrum of cGAS has markedly expanded in recent years, to include sensing capabilities beyond classical dsDNA. For example, DNA–RNA hybrids are a recently identified class of ligands recognized and activated by cGAS. These hybrids typically accumulate in malignant cells as a result of replication-stress-induced R-loops or aberrant transcription of endogenous retroelements[18,21]. Additionally, although cGAS is not directly triggered by single-stranded RNA, its signaling axis is subject to complex regulation by various RNA species; for example, specific endogenous circular RNAs physically interact with cGAS and modulate its activation state. Notably, extensive functional crosstalk exists between the cGAS–STING cascade and RNA-sensing

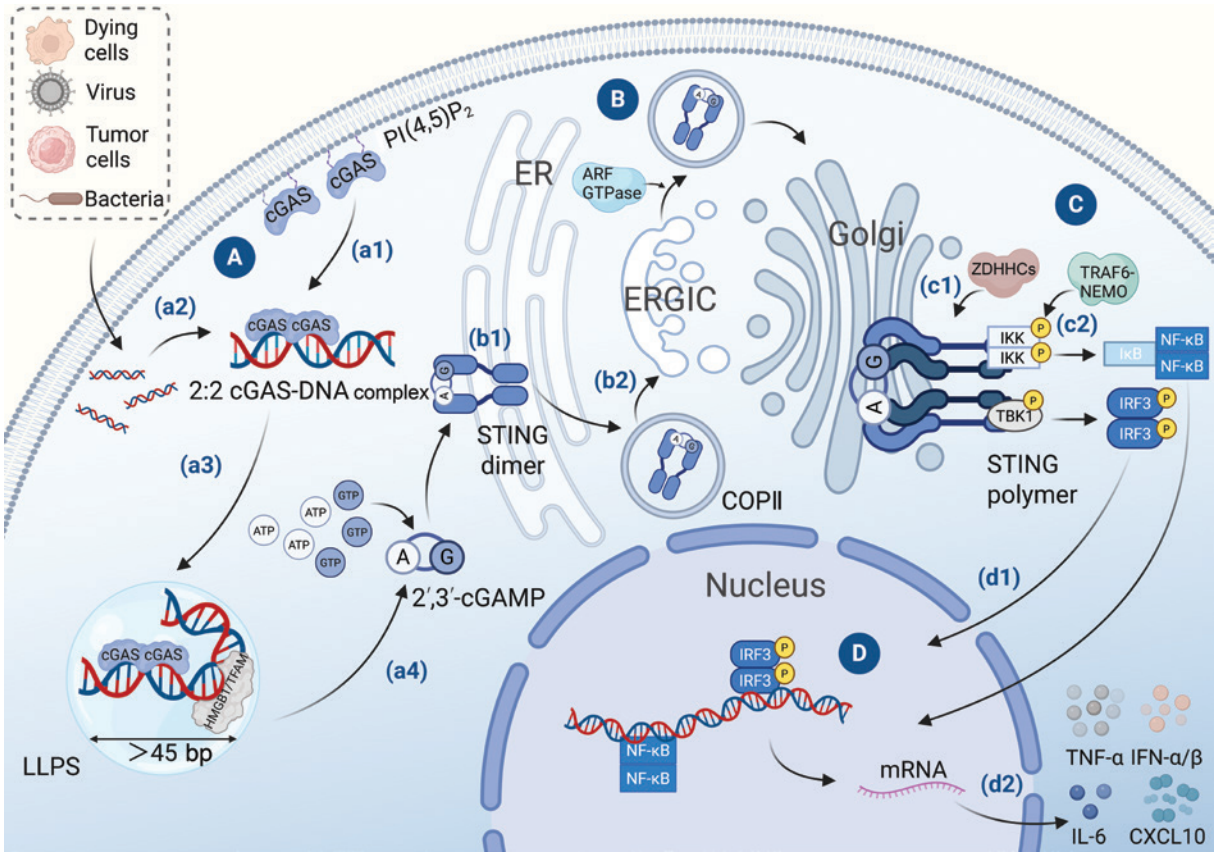


Figure 1 Molecular activation and signaling cascades of the cGAS–STING pathway. This figure illustrates the complete signaling process of the cGAS–STING pathway from cytosolic DNA sensing to nuclear gene transcription. (A) cGAS activation and cGAMP synthesis (cytosol): In the resting state, cGAS is tethered to the plasma membrane inner leaflet through interaction with $PI(4,5)P_2$ (a1). After recognizing aberrant dsDNAs derived from tumor cells, viruses, or bacteria, it dissociates from the membrane and opens its catalytic pocket, thus driving the zinc-finger-dependent assembly of the active 2:2 cGAS–DNA complex (a2). In the case of long DNA strands (>45 bp), the complex further matures, with assistance from architectural proteins (TFAM and HMGB1) and subsequently induces the formation of ladder-like oligomers and LLPS (a3), which lead to spatial confinement optimizing the enzymatic synthesis of the second messenger 2′,3′-cGAMP from ATP and GTP substrates (a4). (B) STING activation and trafficking (ER to Golgi): cGAMP binds the preformed STING dimer on the ER and induces a stable closed conformation (b1). STING is packaged into COPII vesicles and translocated to the Golgi apparatus *via* the ERGIC, in a process regulated by ARF GTPases (b2). (C) Signalosome assembly and kinase recruitment (Golgi): At the Golgi, STING undergoes palmitoylation mediated by ZDHHCs and forms higher-order polymers (c1), which recruit and activate IKK *via* the TRAF6–NEMO complex, thus inducing NF-κB release; as well as TBK1, thus leading to IRF3 phosphorylation (c2). (D) Nuclear transcription and immune output (nucleus): Phosphorylated NF-κB and IRF3 are translocated into the nucleus (d1), where they synergistically drive the transcription and secretion of IFN-I and proinflammatory cytokines (TNF-α, IL-6, and CXCL10), thereby initiating antitumor immune responses (d2). ARF, ADP-ribosylation factor; ATP, adenosine triphosphate; cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; COPII, coat protein complex II; CXCL10, C-X-C motif chemokine ligand 10; dsDNA, double-stranded DNA; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment; GTP, guanosine triphosphate; HMGB1, high mobility group box 1; IFN, interferon; IκB, inhibitor of NF-κB; IKK, IκB kinase; IL-6, interleukin 6; IRF3, interferon regulatory factor 3; LLPS, liquid-liquid phase separation; mRNA, messenger RNA; NEMO, NF-κB essential modulator; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; $PI(4,5)P_2$, phosphatidylinositol 4,5-bisphosphate; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; TFAM, mitochondrial transcription factor A; TNF-α, tumor necrosis factor-α; TRAF6, TNF receptor-associated factor 6; ZDHHCs, zinc finger DHHC-type palmitoyltransferases. (Figure created with BioRender, www.biorender.com).

mechanisms. STING participates in the signaling of the RNA sensor retinoic acid-inducible gene I (RIG-I); moreover, both cGAS and STING play critical roles during RNA viral infection and the subsequent viral blockade of type I interferon (IFN-I) induction[22,23]. These intricate interconnections suggest that the cGAS–STING pathway is not merely a simple DNA sensor but a comprehensive hub integrating diverse nucleotide-associated stress signals.

Signal transduction: STING activation, conformational changes, and Golgi translocation

Conformational changes and subcellular translocation of the STING protein are the core steps in its signal activation. This process involves structural rearrangement from a static endoplasmic reticulum (ER)-resident state to a dynamic signaling complex. After the recognition of aberrant DNA by cGAS and subsequent generation of the second messenger cGAMP, cGAMP binds and activates the STING protein on the ER membrane[24]. The activation of STING, a critical signaling hub on the ER membrane, relies on multilevel conformational changes and alterations in its subcellular localization.

The STING protein consists of a short N-terminal cytoplasmic segment, four transmembrane (TM) helices, a central ligand-binding domain (LBD), and a C-terminal tail (CTT). After cGAMP binds the LBD of STING, the STING dimer adopts a stable "closed conformation," which triggers a cascade of events leading to its translocation from the ER to the Golgi apparatus[17,25,26], in a process dependent on the coat protein complex II (COPII) vesicular transport system. STING is initially packaged into the ER–Golgi intermediate compartment (ERGIC) *via* the COPII complex and subsequently localizes to the Golgi apparatus under the regulation of ADP-ribosylation factor (ARF) GTPase[27,28] (**Figure 1B**). Structural biology studies have revealed that during translocation, the LBD of STING undergoes rotation and rearrangement. Its cytoplasmic linker region, including the TM2–TM3 loop, mediates interactions between dimers, and subsequently leads to the formation of tetrameric and higher-order oligomeric platforms that are crucial for recruiting and activating the downstream TANK-binding kinase 1 (TBK1)[14,20,29].

The Golgi localization of STING is closely associated with its post-translational modifications. In the Golgi apparatus, STING undergoes palmitoylation at Cys88 and Cys91. This lipid modification promotes STING clustering and downstream signaling, ultimately stabilizing the activated STING signaling complex; in addition, it provides a temporal and spatial window for the sustained recruitment and activation of TBK1[25,30]. Notably, the degree of STING oligomerization directly influences the intensity of signal output. Cryo-electron microscopy studies have revealed that after the formation of helical tetramers and higher-order oligomers at the Golgi, the exposure of the CTT domain of STING creates a docking space for TBK1 dimers[29,31]. This conformational change simultaneously exposes phosphorylation sites on STING, thereby promoting TBK1-mediated autophosphorylation and forming a positive feedback loop resulting in signal amplification[16,32]. Mutations at the palmitoylation sites of STING markedly inhibit downstream signaling, thus highlighting the critical role of this modification in the signaling cascade. At the Golgi apparatus, STING palmitoylation and oligomerization constitute a synergistic regulatory mechanism, with zDHHC palmitoyltransferase 1 (ZDHHC1) serving as a positive regulator of STING signaling[17,33] (**Figure 1C**). These precise conformational changes and subcellular localization dynamics collectively ensure the signal fidelity of the cGAS–STING pathway from DNA recognition to immune effector activation, thus laying the structural foundation for subsequent activation of the TBK1–interferon regulatory factor 3 (IRF3) signaling axis.

Signal output: coordinated activation of downstream pathways and immune effects

After STING translocation to the Golgi apparatus and palmitoylation, the conserved PLPLRT/SD motif within the CTT of STING serves as a critical platform for direct recruitment of TBK1[34,35]. TBK1 binds this motif on the STING dimer *via* its C-terminal coiled-coil domain, and subsequently triggers TBK1 autophosphorylation (at Ser172) and transphosphorylation[32]. Activated TBK1 does not phosphorylate the entire STING CTT but specifically targets the pLxIS motif within STING, particularly the serine residue at position 366 (Ser366) in humans. Moreover, the phosphorylated pLxIS motif itself transforms into a new platform for recruiting the downstream transcription factor IRF3. Subsequently, TBK1 within the same signaling complex further catalyzes the phosphorylation of IRF3 at Ser386/Ser396, and consequently induces IRF3 homodimerization and nuclear translocation[36]. Concurrently, STING activates the IκB kinase (IKK) complex *via* the TNF receptor-associated factor 6 (TRAF6)–NF-κB essential modulator (NEMO) complex, thus leading to the phosphorylation and degradation of IκBα. This process releases the NF-κB dimer (p50/RelA) for nuclear import[21,37] (**Figure 1C**). In the nucleus, the phosphorylated IRF3 dimer cooperates with NF-κB at specific gene promoter regions in driving the expression of IFN-I (IFN-α/β) and inflammatory cytokines/chemoattractants, such as tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and C-X-C motif chemokine ligand 10 (CXCL10) (**Figure 1D**). Notably, chronic STING activation induces the noncanonical NF-κB pathway (p52/RelB) and promotes sustained expression of proinflammatory factors[15]. These secreted molecules in turn initiate both innate and adaptive immune responses, thus effectively clearing pathogens or abnormal cells and exerting anti-infective and antitumor effects.

Signal termination and negative feedback regulatory mechanisms

Timely termination of the STING pathway relies on multilayered regulatory mechanisms. First, the STING adaptor protein undergoes polyubiquitination mediated by E3 ubiquitin ligases and is subsequently degraded *via* the lysosomal pathway, thereby achieving prompt clearance of signaling elements[31].

Furthermore, after STING fulfills its role in recruiting and activating TBK1–IRF3, rephosphorylation of its Ser366 residue triggers negative feedback on the IRF3 signal. Finally, the hydrolysis of extracellular cGAMP by ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1)[38,39] prevents STING activation in neighboring immune cells and therefore prevents the activation of antitumor immune responses.

Dual roles of the cGAS–STING pathway in tumor immune regulation

The precise activation and termination mechanisms of the cGAS–STING pathway ensure the appropriateness and controllability of its response. However, within the complex context of the TME, the function of this pathway exhibits a notable duality.

First, activation of the cGAS–STING pathway, a central sensor of innate immunity, induces the production of IFN-I and inflammatory factors, and consequently promotes antitumor immune responses. However, further research and new evidence[40,41] have indicated that the cGAS–STING signaling cascade might play dichotomous roles in tumor development. In certain contexts, highly aggressive and genomically unstable tumors can paradoxically stimulate oncogenesis through cGAS/STING signaling[42].

Antitumor immune effects

Analysis of 18 types of malignant tumors in The Cancer Genome Atlas multicancer data has revealed significantly greater expression of four key cGAS–STING pathway genes (*MB21D1* encoding cGAS, *TMEM173* encoding STING, *TBK1*, and *IRF3*) in almost all examined cancer types than in corresponding normal tissues; these findings suggest potentially widespread activation of this pathway in cancer[43]. However, because these analyses relied on bulk RNA sequencing, these elevated transcripts are likely to reflect the dense infiltration of host immune cells within the microenvironment rather than an origin from exclusively tumor cells. Notably, the formation of tertiary lymphoid structures (TLSs, organized aggregates of immune cells that are increasingly recognized as critical sites for antitumor immunity) is likely to be a major anatomical source of these elevated transcripts[44]. This aspect is important, given that recent studies suggest an intricate biological link, wherein STING pathway activation in the microenvironment actively promotes the neogenesis of these TLSs[45-47]. Furthermore, although this pan-cancer study demonstrated that the expression of these pathway genes exhibits complex, context-dependent correlations with immune infiltration, displaying both positive and negative associations depending on the specific cancer type[43], a predominant body of evidence underscores the critical role of this pathway in driving antitumor immune surveillance. Specifically, when effectively activated, the cGAS–STING cascade initiates robust antitumor responses through both tumor-cell-intrinsic and immune-cell-intrinsic mechanisms. Cancer cells bearing chromosomal abnormalities or genomic DNA damage often form micronuclei or cytoplasmic chromatin fragments, which subsequently activate cGAS in a cell-autonomous manner and initiate the downstream signaling cascade. This process subsequently enhances adaptive anticancer immunity, inhibits or eliminates cancer cells, induces cellular senescence, and promotes autophagy (**Figure 2**, **left**).

Beyond autonomous activation within cancer cells, this mechanism operates within immune cells in the TME. After dendritic cells (DCs) take up DNA fragments from the TME, the DC-intrinsic STING pathway is activated. Subsequently, a robust IFN-I response promotes their maturation and uniquely licenses these antigen-presenting cells (APCs) for the cross-presentation of tumor antigens, thereby activating antitumor $CD8^+$ T cells (**Figure 2, left**). Furthermore, this pathway directly recruits and activates natural killer (NK) cells by inducing the expression of chemoattractants and natural killer group 2D (NKG2D) ligands, which act synergistically with T cells in mediating a potent antitumor immune response[48] (**Figure 2, left**).

Moreover, the cGAS–STING pathway regulates cell fate through multiple mechanisms. Zierhut et al.[49] have proposed that the cGAS pathway inhibits B-cell lymphoma-extra large (Bcl-xL) through the gradual accumulation of phosphorylated IRF3, thereby inducing mitochondrial pathway apoptosis in tumor cells undergoing mitotic arrest. The STING pathway itself also upregulates expression of the proapoptotic Bcl-2-associated X (Bax) protein and activates the caspase-9/caspase-3 cascade, which in turn executes the apoptotic program[50] (**Figure 2, left**). Regarding cellular senescence, Dou et al.[51] have used a RasVal12 expression vector to induce liver tumors and found that STING-deficient mice exhibit diminished early immune cell infiltration and clearance of senescent cells. A dual regulatory relationship exists between the cGAS–STING pathway and autophagy: the pathway triggers autophagy through various means, whereas autophagy regulates the cGAS–STING pathway *via* a feedback loop[52].

Immune evasion and protumor effects

Beyond the aforementioned antitumor immune surveillance functions, abnormal or sustained cGAS–STING pathway activation promotes tumor progression. This protumor effect manifests primarily in three ways: the formation of an immunosuppressive TME, the induction of treatment resistance, and the promotion of tumor metastasis.

First, chronic and aberrant activation of the cGAS–STING pathway actively orchestrates the formation of an

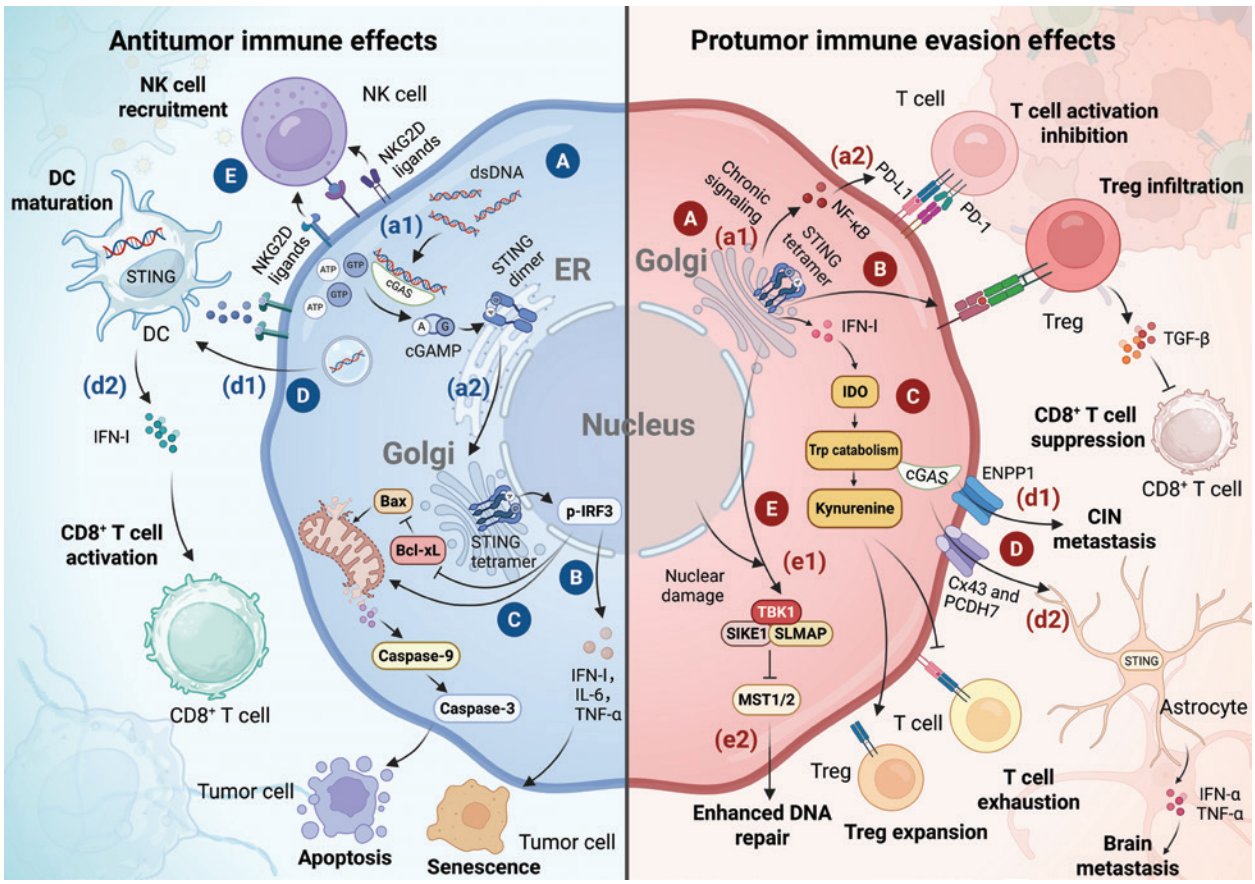


Figure 2 Bidirectional regulation of the tumor microenvironment by the cGAS–STING signaling pathway. This schematic illustrates the dual nature of cGAS–STING signaling, involving opposing roles in fostering antitumor immunity *vs.* facilitating tumor progression and immune evasion. (Left) Antitumor immune effects: Activation of the canonical pathway triggers innate and adaptive immune responses along with direct tumor cell death. (A) cGAS–STING activation: After sensing of cytosolic dsDNA by cGAS, the second messenger cGAMP (a1) is generated. cGAMP binds the STING dimer at the ER and triggers its translocation to the Golgi apparatus and subsequent polymerization (a2). (B) Cytokine induction: The activated STING complex recruits TBK1 and promotes formation of phosphorylated IRF3 (p-IRF3), which translocates to the nucleus and induces the expression of IFN-I, IL-6, and TNF-α. These cytokines subsequently induce tumor cell senescence. (C) Cell death mechanisms: Beyond cytokine release, STING activation directly triggers tumor cell apoptosis *via* the upregulation of Bax, inhibition of Bcl-xL, and activation of the caspase-9/caspase-3 cascade. (D) Immune recruitment: After uptake of DNA fragments from the TME by DCs, activation of the intrinsic STING pathway (d1) induces an IFN-I response, which promotes DC maturation and activation of antitumor CD8⁺ T cells (d2). (E) NK cell recruitment: The upregulation of NKG2D ligands recruits NK cells to tumor sites. (Right) Protumor immune evasion effects: Chronic or noncanonical signaling within the TME creates an immunosuppressive niche and promotes metastasis. (A) Immunosuppression: Nuclear damage activates STING, which in turn stimulates NF-κB *via* noncanonical or chronic signaling (a1). Upregulation of PD-L1 expression leads to the inhibition of T cell activation *via* the PD-1 axis (a2). (B) Immunosuppression: The pathway promotes Treg infiltration and TGF-β secretion and ultimately leads to the suppression of CD8⁺ T cells. (C) Immunosuppression: The induction of IDO metabolizes tryptophan into kynurenine, thereby resulting in the suppression of T cell function and the expansion of Tregs. (D) Metastasis promotion: The pathway facilitates the metastasis of CIN tumors *via* ENPP1-mediated hydrolysis of extracellular cGAMP (d1). Furthermore, Cx43 and PCDH7 mediate intercellular communication and transfer of cGAMP to astrocytes, thus activating the STING pathway, inducing IFN-α and TNF-α secretion, and promoting brain metastasis (d2). (E) Therapeutic resistance: STING activation stabilizes the STRIPAK assembly (containing TBK1, SIKE1, and SLMAP), which inhibits MST1/2 kinase activity (e1) and leads to enhanced DNA repair and augmented tumor capability for DNA damage repair (e2). ATP, adenosine triphosphate; Bax, Bcl-2-associated X protein; Bcl-xL, B-cell lymphoma-extra large; CD, cluster of differentiation; cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; CIN, chromosomal instability; Cx43, connexin 43; DC, dendritic cell; dsDNA, double-stranded DNA; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; ER, endoplasmic reticulum; GTP, guanosine triphosphate; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL-6, interleukin 6; IRF3, interferon regulatory factor 3; MST1/2, mammalian STE20-like kinase 1/2; NF-κB, nuclear factor

kappa-light-chain-enhancer of activated B cells; NK, natural killer; NKG2D, natural killer group 2D; PCDH7, protocadherin 7; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SIKE1, suppressor of IKK epsilon 1; SLMAP, sarcolemma-associated protein; STING, stimulator of interferon genes; STRIPAK, striatin-interacting phosphatase and kinase; TBK1, TANK-binding kinase 1; TGF-β, transforming growth factor-β; TME, tumor microenvironment; TNF-α, tumor necrosis factor-α; Treg, regulatory T cell. (Figure created with BioRender, www.biorender.com.)

immunosuppressive TME through both immune-cell-mediated and tumor-cell-intrinsic mechanisms. Within the immune compartment, persistent STING signaling promotes the infiltration and function of regulatory T cells (Tregs). For example, in human papillomavirus positive cervical cancer, this activation drives accumulation of Tregs, which subsequently impair the antitumor function of $CD8^+$ T cells *via* molecules such as transforming growth factor-β (TGF-β) and lead to poor patient prognosis[53] (**Figure 2, right**). Furthermore, Field et al.[54] have reported that activated cGAS–STING–IFN-I signaling within Tregs intrinsically enhances, rather than weakens, their immunosuppressive capability.

Parallel to these immune-mediated effects, chronic STING activation within tumor cells themselves establishes an immunosuppressive barrier, primarily *via* the IFN-I-dependent indoleamine 2,3-dioxygenase (IDO) pathway[37,55]. Specifically, STING-induced IDO expression drives tryptophan depletion and the accumulation of immunosuppressive kynurenine, which in turn directly impairs effector T-cell function (**Figure 2, right**). Simultaneously, sustained STING signaling induces the expression of programmed death-ligand 1 (PD-L1), thus providing tumor cells with an adaptive feedback mechanism for immune checkpoint evasion[56-58] (**Figure 2, right**).

Collectively, these mechanisms indicate that under chronic stress within the TME, the immunomodulatory function of the cGAS–STING pathway undergoes a critical reversal. By synergistically reinforcing Treg function, rewiring IDO metabolic pathways, and upregulating PD-L1, sustained activation shifts the pathway from driving antitumor immunity to actively facilitating immune evasion.

These findings indicate that the protumorigenic effects of this pathway arise primarily from its chronic activation, which is distinct from the antitumor immune surveillance mediated by acute activation. Therefore, in developing targeted strategies, distinguishing the duration, intensity, and cell-type specificity of activation is essential to achieve precise modulation.

The cGAS–STING pathway also plays a complex role in tumor metastasis. Chen et al.[59] have reported that tumor cells transfer cGAMP to astrocytes *via* connexin 43 (Cx43) and protocadherin 7 (PCDH7), thereby activating the STING pathway in astrocytes and inducing the secretion of IFN-α and TNF-α, which in turn promote the formation of brain metastases. Furthermore, cGAS activation promotes metastasis and immune evasion in tumors with chromosomal instability (CIN) through ENPP1-mediated hydrolysis of extracellular cGAMP and adenosine generation[39]. Therefore, paracrine activation of the cGAS–STING pathway might create a favorable microenvironmental foundation for tumor metastasis (**Figure 2, right**).

Regarding treatment resistance, activation of the cGAS–STING pathway has also been shown to decrease tumor sensitivity to therapy. An et al.[60] have demonstrated that pathway activation stabilizes the suppressor of IKK epsilon 1 (SIKE1)–sarcolemma associated protein (SLMAP) complex in a TBK1-dependent manner, promotes the assembly of the striatin-interacting phosphatase and kinase (STRIPAK)–mammalian STE20-like kinase 1/2 (MST1/2) supramolecular complex, subsequently inhibits MST1/2 kinase activity, and ultimately enhances DNA damage repair capability and decreases treatment sensitivity in tumor cells (**Figure 2, right**).

In summary, the protumorigenic effects of the cGAS–STING pathway arise from the interplay among the immunosuppressive microenvironment, the formation of a premetastatic niche, and the induction of therapeutic resistance. This multifaceted role notably highlights the duality and context dependency of STING signaling, and further underscores the need for future research to use a network regulation perspective to delineate dominant mechanisms across different contexts and to elucidate their synergistic or compensatory relationships.

The duality of cGAS–STING biology: cell-type specificity and context dependency

The antitumor and protumor effects of the cGAS–STING pathway detailed in the previous sections do not exist in isolation; instead, functional outcomes are dictated by the specific cell types, as well as the duration and intensity of activation. Elucidating the determinants of this duality is essential for understanding the heterogeneity of therapeutic efficacy in real-world clinical trials and guiding the formulation of precision intervention strategies.

To dissect the mechanistic differences underlying these effects, we first focus on tumor-intrinsic STING signaling (**Figure 3A**). This signaling exhibits high temporal and intensity dependency. After acute activation, it coordinates a chemokine program that recruits peripheral T cells[61]. In contrast, chronic, low-grade STING activation, triggered by CIN

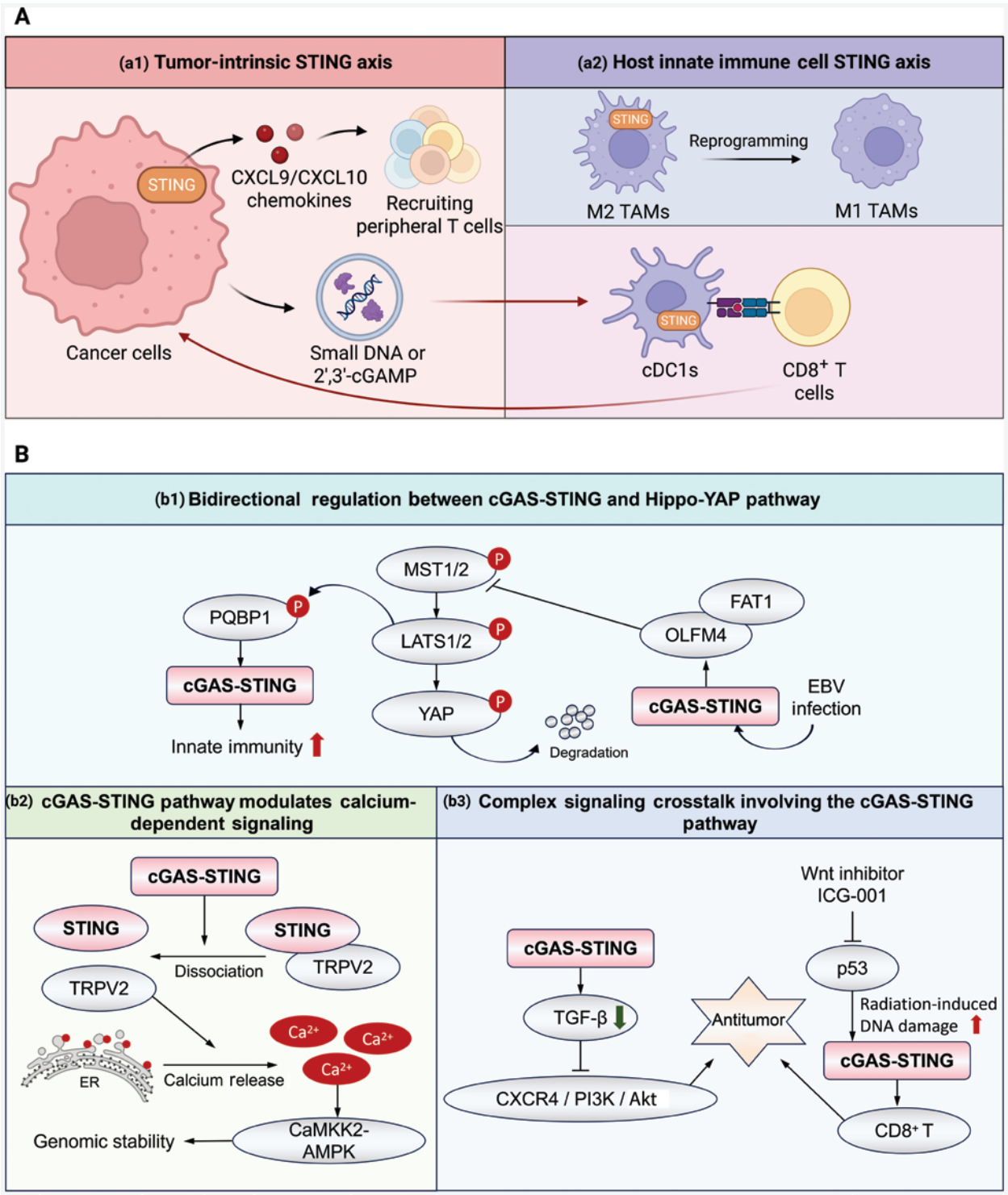


Figure 3 Comparison of the tumor-intrinsic and host innate immune cell STING axes and the complex interactions between the cGAS–STING signaling pathway and multiple oncogenic or tumor-suppressive pathways. This figure illustrates the intricate crosstalk and regulatory networks involving cGAS–STING in the TME. (A) Parallel comparison of the tumor-intrinsic and host innate immune cell STING axes: Tumor-intrinsic STING signaling coordinates a chemokine program upon activation, thus leading to the secretion of CXCL9 and CXCL10, which in turn recruit peripheral T cells into the TME (a1). In TAMs, STING activation forces phenotypic reprogramming from a protumoral M2 to an antitumoral M1 state. The critical intersection of these two parallel pathways occurs *via* cDC1-mediated antigen cross-presentation,

wherein tumor-derived small DNA or synthesized 2′,3′-cGAMP is horizontally transferred to adjacent cDC1s; subsequent intrinsic STING activation within these cDC1s ultimately "licenses" them to cross-present tumor-associated antigens to $CD8^+$ T cells, thereby translating local tumor stress into systemic T-cell-mediated cytotoxicity (a2). (B) Complex interactions between the cGAS–STING signaling pathway and multiple oncogenic or tumor-suppressive pathways: Bidirectional regulation with the Hippo–YAP pathway: LATS1/2 enhances cGAS–STING-mediated innate immunity by phosphorylating PQBP1, whereas EBV infection activates the cGAS–STING pathway and leads to upregulation of OLFM4, which in turn binds FAT1 and disrupts the Hippo kinase complex (MST1/2–LATS1/2), thereby activating YAP and promoting tumor progression (b1). Modulation of calcium-dependent signaling: The cGAS–STING product cGAMP promotes STING dissociation from the TRPV2 channel, thus triggering release of calcium from the ER and subsequent activation of the downstream CaMKK2–AMPK signaling axis, thereby maintaining genomic stability during replication stress (b2). Signaling crosstalk with oncogenic pathways: Activated STING downregulates TGF-β and leads to inhibition of the CXCR4/PI3K/Akt axis, thus decreasing tumor metastasis; additionally, the Wnt inhibitor ICG-001 inhibits p53 and subsequently increases radiation-induced DNA damage, thereby activating cGAS–STING signaling and enhancing $CD8^+$ T-cell-mediated antitumor immunity (b3). Akt, protein kinase B; AMPK, AMP-activated protein kinase; CaMKK2, calcium/calmodulin-dependent protein kinase kinase 2; CD, cluster of differentiation; cDC1, type 1 conventional dendritic cell; cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; CXCL9/10, C-X-C motif chemokine ligand 9/10; CXCR4, C-X-C motif chemokine receptor 4; EBV, Epstein–Barr virus; ER, endoplasmic reticulum; FAT1, FAT atypical cadherin 1; LATS1/2, large tumor suppressor kinase 1/2; MST1/2, mammalian STE20-like kinase 1/2; OLFM4, olfactomedin 4; PI3K, phosphoinositide 3-kinase; PQBP1, polyglutamine-binding protein 1; STING, stimulator of interferon genes; TAM, tumor-associated macrophage; TGF-β, transforming growth factor-β; TME, tumor microenvironment; TRPV2, transient receptor potential vanilloid 2; YAP, Yes-associated protein. (Figure created with BioRender, www.biorender.com.)

and aberrant cytosolic DNA, drives T-cell dysfunction and exhaustion, thus prompting the tumor to establish immunosuppressive feedback loops, such as the compensatory upregulation of PD-L1 and IDO[55,56]. Furthermore, this sustained DNA-damage-induced chronic STING activation can be "hijacked" by tumor cells to promote the epithelial–mesenchymal transition, and consequently accelerate tumor metastasis and progression[62,63].

Outside tumor cells, the STING axis within host innate immune cells is a critical driver of durable adaptive antitumor immunity. In tumor-associated macrophages (TAMs), STING activation forces a phenotypic reprogramming from a protumoral M2 to an antitumoral M1 state[64,65]. This potent immunostimulatory capability is a hallmark of immune-cell-intrinsic STING activation, a feature largely absent in tumor cells.

The critical juncture of these two parallel pathways lies in type 1 conventional dendritic cell (cDC1)-mediated antigen cross-presentation[66]. Tumor-derived DNA or synthesized 2′,3′-cGAMP is horizontally transferred to adjacent cDC1s[67]. The subsequent intrinsic STING activation within these cDC1s ultimately "licenses" them to cross-present tumor-associated antigens to $CD8^+$ T cells, thereby translating local tumor stress into systemic T-cell-mediated cytotoxicity[68] (**Figure 3A**).

Consequently, tumor-intrinsic acute STING activation initiates the early immune cascade, whereas host cDC1- and macrophage-intrinsic STING signaling amplifies these subsequent effects, thus driving durable antitumor immunity. Therefore, in clinical translation, the duration and intensity of activation must be rigorously controlled to avoid the chronic activation state that triggers immunosuppression and therapeutic resistance.

Close interaction of the cGAS–STING pathway with multiple oncogenic or tumor suppressive pathways

The cGAS–STING pathway engages in complex crosstalk with multiple signaling pathways within the TME, and consequently influences tumorigenesis and progression. Recent studies have revealed a bidirectional interaction between the cGAS–STING pathway and the Hippo–Yes-associated protein (YAP) signaling cascade: large tumor suppressor kinase 2 (LATS2), a core kinase of the Hippo pathway, enhances cGAS–STING-mediated innate immunity and suppresses human immunodeficiency virus 1 (HIV-1) infection by phosphorylating polyglutamine-binding protein 1 (PQBP1)[69]. In contrast, Epstein–Barr virus (EBV) infection activates the cGAS–STING pathway and consequently upregulates olfactomedin 4 (OLFM4), which in turn disrupts the Hippo kinase complex by binding FAT atypical cadherin 1 (FAT1) and ultimately activates YAP, a protein that promotes tumor progression[70] (**Figure 3B**). Furthermore, the cGAS–STING pathway is associated with calcium signaling and metabolic pathways: Li et al.[71] have reported that the cGAS–STING pathway, *via* its product cGAMP, promotes the dissociation of STING from the calcium channel transient receptor potential vanilloid 2 (TRPV2), and triggers ER calcium release. Subsequent activation of the downstream Ca^{2+}/calmodulin-dependent protein kinase kinase 2–AMP-activated protein kinase (CaMKK2–AMPK) signaling axis maintains genomic stability during replication stress (**Figure 3B**). This pathway also functionally interacts with crucial oncogenic signals such as phosphoinositide 3-kinase (PI3K) and Wnt. Lu et al.[72] have reported that cGAMP-activated STING downregulates TGF-β, thus inhibiting the C-X-C motif chemokine receptor 4 (CXCR4)/

PI3K/protein kinase B (Akt) axis and decreasing metastasis in triple-negative breast cancer (BC). In contrast, Pang et al.[73] have reported that the Wnt/β-catenin pathway inhibits cGAS–STING signaling. Huang et al.[74] have further confirmed that the Wnt inhibitor ICG-001 increases radiation-induced DNA damage and cGAS–STING pathway activation by inhibiting p53, and ultimately enhances $CD8^+$ T-cell infiltration and antitumor immunity (**Figure 3B**). Collectively, by revealing the intricate interactions between the cGAS–STING pathway and multiple signaling pathways in the TME, these studies have provided novel perspectives for understanding its biological functions and developing combination targeting strategies.

Notably, whereas the aforementioned studies highlighted the diverse interactions of the cGAS–STING pathway, the crosstalk with Hippo signaling reveals a complex duality: cGAS–STING is positively regulated by LATS2, thus bolstering immune responses, yet it can also be co-opted *via* an OLFM4-mediated mechanism, thus suppressing Hippo kinase activity and activating protumorigenic YAP signaling. This divergence is likely to stem from the specific nature of the upstream stimuli, such as viral infection *vs.* physiological stress. Similarly, in its association with the canonical oncogenic PI3K and Wnt pathways, cGAS–STING exhibits a multifaceted role: it exerts tumor-suppressive functions by antagonizing the PI3K/Akt axis and is simultaneously subject to negative regulation by Wnt signaling, an inhibitory effect further sensitized by Wnt inhibitors. Collectively, these bidirectional regulatory networks suggest that the ultimate functional consequence of cGAS–STING activation is not an inherent attribute but is contextually determined by both the nature of the primary stimulus and the specific signaling environment in which it operates.

The cGAS–STING pathway: a critical hub regulating the dynamic interconversion of "cold" and "hot" tumors

As a critical bridge connecting innate immunity and adaptive immunity, the cGAS–STING pathway acts as a dual switch in tumor immunity: its timely activation initiates antitumor immunity, whereas its aberrant chronic activation leads to immunosuppression, metastasis, and treatment resistance. This complex bidirectional regulatory property makes the cGAS–STING pathway a core factor influencing the state of the tumor immune microenvironment and a key hub regulating the dynamic interconversion between "cold" and "hot" tumors.

Definition and immunological characteristics of cold *vs.* hot tumors

The TME is a highly dynamic and heterogeneous ecosystem. Because its complexity stems not only from cellular composition but also from the diversity of spatial architecture and intercellular interactions, it poses substantial cancer immunotherapy challenges. This heterogeneity is particularly evident in the classification of tumors by degree of immune cell infiltration: (i) "immune desert," characterized by a near-complete absence of immune cells within the tumor parenchyma; (ii) "immune excluded," characterized by TILs that are confined to the tumor periphery or stroma and cannot effectively infiltrate the parenchymal region; and (iii) "immune inflamed," characterized by substantial infiltration of immune cells into the core region, accompanied by abundant effector molecules/proinflammatory cytokines. Typically, the immune-desert and immune-excluded subtypes are collectively referred to as "cold" tumors (or immunologically cold tumors), whereas the immune-inflamed subtype was considered a "hot" tumor (or immunologically "hot" tumor)[7,75]. Notably, TME heterogeneity exists not only among cancer types but also among patients with the same cancer type or among tumor lesions in the same patient[76]. To guide clinical translation and avoid conceptual discontinuity, this descriptive classification must be replaced by an actionable stratification based on specific translatable decision elements, which dictate the rational selection of targeted therapies.

Cold tumors

Cold tumors are characterized primarily by an immunosuppressive TME, which manifests in the following four translatable dimensions:

1. Sparse spatial distribution of TILs: The "immune-desert" state has a near-complete absence of CTLs and NK cells across the tumor bed, whereas in the "immune-excluded" state, TILs are largely restricted to the invasive margin and do not penetrate the tumor core[77].
2. High magnitude of myeloid suppression: The microenvironment is enriched in Tregs and characterized by marked accumulation of myeloid-derived suppressor cells (MDSCs) and M2-type TAMs. These cells, by secreting inhibitory cytokines such as IL-10 and TGF-β, establish a potent biochemical barrier that dampens immune cell activity[78].
3. Absence of IFN-γ/IFN-I gene signatures: These signatures, reflecting critically low tumor immunogenicity, are typically accompanied by a low tumor mutational burden (TMB), defective antigen presentation [e.g., downregulation of major histocompatibility complex (MHC)-I], and insufficient expression of immune checkpoints such as PD-L1[79].
4. Rigid vascular and stromal barriers: Dense extracellular matrix (ECM) and disorganized, aberrant vascular architectures collectively form robust physical barriers that severely impede drug delivery and hinder T-cell infiltration into the tumor parenchyma[80].

Hot tumors

In contrast, hot tumors exhibit an "immune-inflamed" phenotype. Key actionable features include the following:

1. Favorable spatial distribution of TILs: The tumor core is densely infiltrated by abundant $CD8^+$ T cells and NK cells, and TLSs can form[81], thus providing local support for adaptive immune responses.
2. Robust *IFN-γ*/IFN-I gene signatures: Active immune signaling pathways, particularly those involving IFN-γ and inflammatory cytokines such as CXCL9/10, are markedly upregulated[77], thereby indicating an active state of immune recognition and effector function.
3. High tumor immunogenicity: These tumors typically have a high TMB and neoantigen load, which promote DC activation and subsequently initiate T-cell-mediated immune responses[78].

Core mechanisms through which the cGAS–STING pathway drives the cold-to-hot transformation of tumors

The cGAS–STING pathway is a critical bridge connecting innate immunity and adaptive immunity, and its activation status extensively influences tumor immune phenotype. In typical "hot" tumors, such as melanoma[82] and gastric cancer with high microsatellite instability[83], this pathway is generally highly activated. These tumors already exhibit T-cell infiltration; therefore, when ICIs are administered, preactivated T cells may rapidly exert their effects. This mechanism partially explains the efficacy of programmed cell death protein 1 (PD-1)/PD-L1 inhibitors in the treatment of these immune-infiltrated malignancies.

Although robust cGAS–STING activation drives a "hot" immune phenotype, this state does not universally translate to clinical responsiveness to ICIs. A substantial proportion of patients with highly infiltrated tumors still experience primary or acquired resistance[84]. This paradox arises because while STING signaling orchestrates indispensable initial T-cell recruitment, chronic activation concurrently triggers potent negative feedback loops. Consequently, a STING-driven inflamed microenvironment is a critical prerequisite, but not a guarantee, of immunotherapy efficacy, and the ultimate clinical outcome largely depends on the activation pattern, duration, and the balance of downstream signaling.

In contrast, in "cold" tumors, this pathway is often inactivated because of functional inhibition, epigenetic silencing, or ineffective activation (**Figure 4**, **left**). How to transform immunologically quiescent "cold" tumors into immunologically active "hot" tumors to enhance their responsiveness to ICIs is a crucial but challenging topic. One core strategy to achieve this transformation is effective activation of the cGAS–STING pathway[85]. The principal mechanisms driving the cold-to-hot transformation are as follows.

Direct activation of innate immune cells

DCs maturation and cross-presentation

Building on the canonical signaling cascade detailed in Section 1.3, the subsequent STING-driven secretion of IFN-I is the primary driver of DC maturation[11]. Rather than merely acting as an inflammatory amplifier, IFN-I mechanistically upregulates crucial surface costimulatory molecules (CD80, CD83, and CD86) and MHC complexes on DCs[86]. This process specifically licenses tumor-infiltrating DCs (TIDCs) for optimal antigen cross-presentation. The density and functional maturity of these TIDCs are critical determinants of the magnitude of the resulting $CD8^+$ T-cell response and ultimately differentiate an immune-reactive "hot" core from an excluded "cold" margin.

DCs are a specialized APC type. After tumorigenesis, they infiltrate solid tumors and form TIDCs. TIDCs present tumor antigens to T cells, thereby promoting the cancer-immunity cycle. The composition of TIDCs varies among tumor types and directly influences the strength of the antitumor T-cell response[87]. Tumors with higher levels of DC infiltration typically exhibit better responses to immunotherapy. Furthermore, TIDCs exhibit diverse functional states, which are important in determining the "cold" or "hot" status of the tumor immune microenvironment and the resulting antitumor immune response[88,89].

Driving the polarization of TAMs toward the M1 phenotype

TAMs within the TME typically exhibit an immunosuppressive M2 phenotype. Targeted modulation of phagolysosomal processing offers a novel approach to overcoming this innate immune barrier. Shang et al.[90] have developed a TAM-targeting nanoscale carrier. By delaying the lysosomal degradation of phagocytosed tumor cells, this carrier allows for sustained intracellular sensing of mitochondrial DNA. This targeted intervention specifically rewires TAMs from an immunosuppressive state to a highly proinflammatory M1 phenotype (**Figure 4**) and fundamentally establishes an immunostimulatory foundation for subsequent T-cell responses. Furthermore, the activation of signal transducer and activator of transcription 1 (STAT1) directly upregulates the expression of M1 markers (CD86 and MHC-II) and the proinflammatory cytokines TNF-α and IL-12, while simultaneously suppressing the expression of M2-associated genes. Additionally, Zhu et al.[91] have reported that vanillic acid triggers the STING/TBK1/IRF3 pathway and strongly induces M1 polarization. Because this effect is reversed by the STING antagonist H151 or the M2-inducing factors IL-4 and IL-13, the process is dependent on STING activation[92].

Enhancement of NK cell activity

Knelson et al.[93] have demonstrated that after STING pathway activation, tumor cells and cancer-associated fibroblasts (CAFs) produce large quantities of CXCR3 ligands, which subsequently recruit NK cells migrating toward tumor sites (**Figure 4**). Interestingly, although STING agonists exhibit cytotoxicity toward T cells, they are not highly toxic to NK cells. NK cells can even maintain their viability

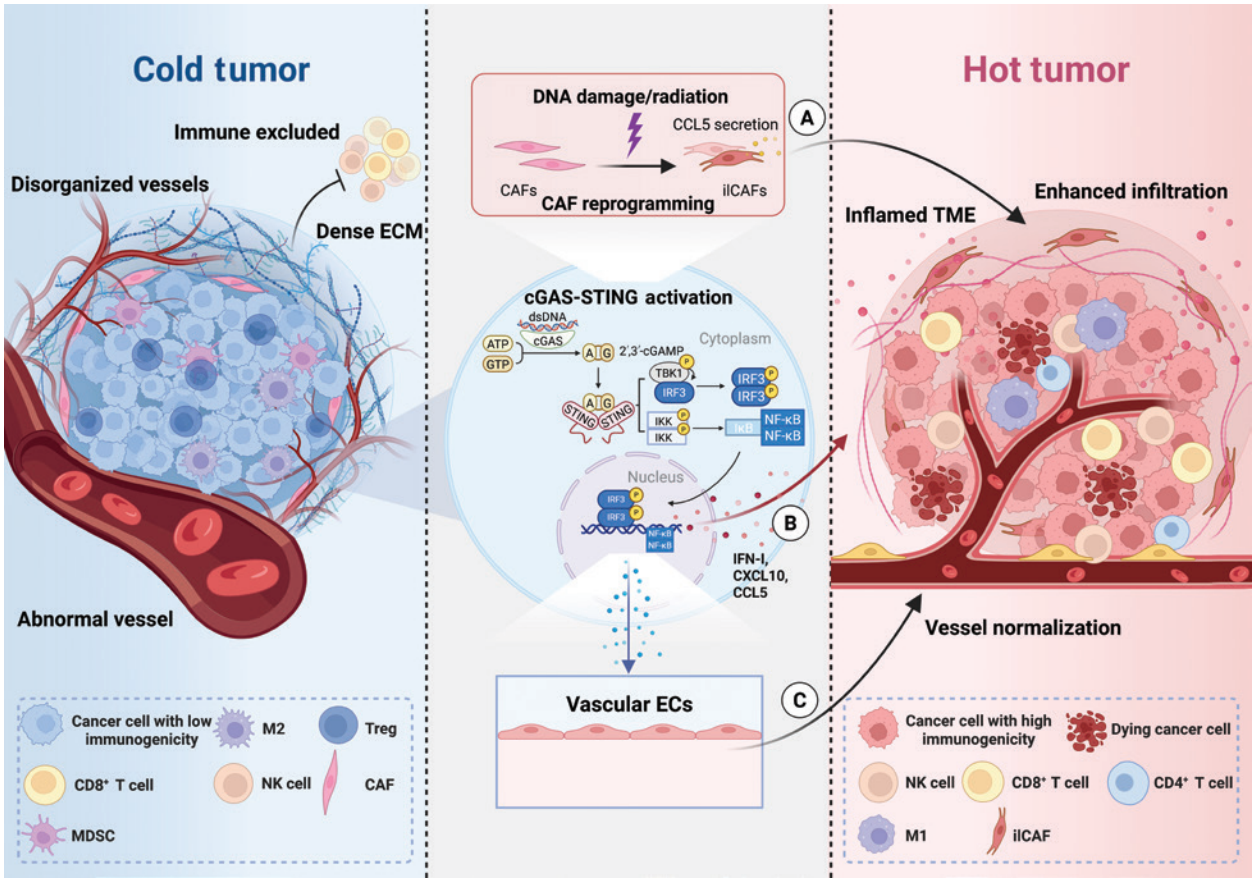


Figure 4 The cGAS–STING pathway is a critical hub driving the cold-to-hot tumor transition. This figure illustrates how the cGAS–STING pathway remodels the TME and consequently shifts immune phenotypes. (Left) Cold tumors: These tumors are characterized by a disorganized vasculature, physical barriers formed by a dense ECM, and the accumulation of immunosuppressive cells (such as M2 macrophages and Tregs), which collectively lead to the exclusion of effector T cells. (Middle) Activation and remodeling: (A) CAF reprogramming: DNA damage or radiation triggers STING activation in CAFs, thus inducing their reprogramming into CCL5-secreting iICAFs that lead to immune cell recruitment. (B) Signaling cascade: Concurrently, within the cytoplasm, cGAS senses DNA and generates 2′,3′-cGAMP, which in turn activates the STING–TBK1–IRF3/NF-κB axis; subsequently, nuclear transcription and the release of IFN-I, CXCL10, and CCL5 amplify immune cell recruitment. (C) Vessel normalization: In vascular ECs, STING activation significantly inhibits abnormal angiogenesis, thereby promoting the normalization of the tumor vascular network. (Right) Hot tumors: The TME transforms into an "inflamed" phenotype featuring vessel normalization, macrophage polarization toward the antitumor M1 phenotype, and extensive infiltration and activation of $CD8^+$ T cells and NK cells. ATP, adenosine triphosphate; CAF, cancer-associated fibroblast; CCL5, C-C motif chemokine ligand 5; CD, cluster of differentiation; cGAMP, cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; CXCL10, C-X-C motif chemokine ligand 10; dsDNA, double-stranded DNA; EC, endothelial cell; ECM, extracellular matrix; GTP, guanosine triphosphate; IFN, interferon; IκB, inhibitor of NF-κB; IKK, IκB kinase; iICAF, interferon-licensed cancer-associated fibroblast; IRF3, interferon regulatory factor 3; M1/M2, macrophage phenotypes; MDSC, myeloid-derived suppressor cell; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer cell; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; TME, tumor microenvironment; Treg, regulatory T cell. (Figure created with BioRender, www.biorender.com.)

under prolonged high-dose exposure. Experiments using a 3D vascular barrier model have further revealed that STING agonists enhance the ability of NK cells to traverse the vascular barrier and migrate toward tumor cells. Lu et al.[94] have reported that STING signaling maintains the T cell factor 1 (TCF-1)$^+$ NK cell pool, thereby enhancing the persistent antitumor capability of these cells. TCF-1$^+$ NK cells possess memory/stem cell-like properties characterized by high proliferative potential and sustained responsiveness. In adoptive NK cell cotransfer competition experiments, the proportion of immature $CD27^+CD11b^-$ cells among *STING*$^{-/-}$ NK cells was significantly lower among tumor-infiltrating NK cells

than co-transferred wild-type NK cells. Furthermore, the expression of TCF-1 in *STING*$^{-/-}$ NK cells was markedly lower than that in wild-type NK cells. Therefore, STING signaling supports the long-term survival and functional maintenance of NK cells within tumors by sustaining the presence of this specific subset.

Indirect and direct regulation of T cells

Indirect synergistic recruitment of effector T cells

Beyond local innate immune licensing, the cold-to-hot transition fundamentally relies on establishing a robust chemotactic gradient (**Figure 4**). Activation of the cGAS–STING pathway induces the expression of CXCL10. As a key chemoattractant, CXCL10, through binding its receptor, CXCR3, effectively recruits CD8$^+$ T cells migrating toward tumor sites. In rigorous preclinical settings, such as the orthotopic mouse liver cancer model established by Fu et al.[95], combined treatment with a STING agonist and cisplatin has successfully amplified this targeted chemokine-driven influx. This combination strategy directly translated to deeply enhanced effector infiltration and concomitant tumor cell apoptosis, as evidenced by elevated cleaved caspase-3 expression. These profound synergistic effects have been validated across multiple tumor models, including MC38 and CT26 mouse colon cancer models[96,97] and the B16 mouse melanoma model[98].

Direct intrinsic effects of STING signaling in T cells

Under physiological conditions or moderate DNA stimulation, the endogenous expression of STING is essential for the maintenance of T-cell function. Emerging evidence suggests that T-cell-intrinsic STING signaling is critical in shaping the differentiation landscape of various T-cell subsets. In CD4$^+$ T cells, STING activation orchestrates T helper 1 (Th1) polarization and enhances effector capability[99]; in contrast, autonomous cGAS–STING signaling in CD8$^+$ T cells promotes differentiation toward a stem-like memory phenotype, a process indispensable for sustaining long-term antitumor immunity[100]. Most importantly, this cell-intrinsic signaling sustains the reservoir of TCF-1$^+$ CD8$^+$ T cells with stem-like features, thus providing the cornerstone for generating durable antitumor immune responses[100].

Notably, effector T cells exhibit hypersensitivity to sustained or high-intensity STING activation. Exposure to high-dose STING agonists disrupts calcium homeostasis, subsequently triggers severe ER stress and the unfolded protein response[101], and culminates in T-cell apoptosis[102]. This fundamental mechanism may contribute to the limited efficacy of some first-generation, systemically administered STING agonists: under nontargeted delivery conditions, these agonists induce the death of effector T cells in both peripheral blood and the TME while simultaneously activating APCs, thereby potentially limiting the overall antitumor efficacy[103].

Remodeling tumor vasculature and stroma

Regulation of the tumor vasculature and immune infiltration

In tumor vascular endothelial cells, activation of the STING pathway substantially inhibits aberrant tumor angiogenesis[10] (**Figure 4, middle**). Yang et al. have further demonstrated that treatment with STING agonists normalizes the inherently disorganized tumor vascular network by upregulating IFN-I and key vascular stabilizing genes, including *Angpt1* and *Pdgfrb*[104]. Furthermore, STING signaling in nonhematopoietic cells, particularly endothelial cells, is a crucial driver of these vascular normalizing effects[105]. After STING activation, tumor blood vessels exhibit enhanced pericyte coverage, restored basement membrane integrity, and upregulated expression of endothelial-leukocyte intercellular and vascular cell adhesion molecules[104]. Ultimately, this functionally normalized vascular architecture establishes an effective conduit for cytotoxic T cells to traverse the endothelial barrier and infiltrate the tumor parenchyma, and subsequently alleviate hypoxia within the TME and profoundly bolster the antitumor immune response[106].

Reprogramming CAFs

CAFs play major roles in tissue homeostasis, tumorigenesis, and the progression of inflammation and fibrosis[107,108]. Through metabolic reprogramming, CAFs secrete various cytokines or metabolites that suppress immune cell function, and promote tumor development, invasion, and metastasis. Furthermore, CAFs shape the ECM by forming a barrier that impedes the penetration of drugs or therapeutic immune cells, and prevents their deep infiltration into tumor tissue, thereby decreasing tumor therapy efficacy[109-113].

A recent study by Huang et al.[114] has revealed that, in colorectal cancer (CRC), activation of the cGAS–STING pathway reprograms CAFs, thereby reversing the inhospitable environment and converting tumors from "cold" to "hot." Radiation-therapy-induced DNA damage activates the STING pathway, which, through downstream signaling involving STAT1 phosphorylation and upregulation of IRF1, promotes the polarization of CAFs into IFN-licensed CAFs (ilCAFs) (**Figure 4, middle**). These ilCAFs secrete the chemoattractants C-C motif chemokine ligands 4 (CCL4) and 5 (CCL5), which in turn bind the C-C chemokine receptor type 5 (CCR5) on the surfaces of T cells and DCs, and subsequently promote immune cell infiltration and achieve conversion of the immune microenvironment from "cold" to "hot."

Reversal of the immunosuppressive microenvironment

Activation of STING in DCs effectively downregulates Tregs. Nguyen et al.[66] have developed the nanovaccine, Si9GM, which precisely activates the STING pathway in cDC1s. This vaccine markedly enhances the efficiency of antigen cross-presentation, induces an IFN-I response, and leads to remodeling of

the tumor immune microenvironment. This process inhibits Tregs while enhancing the antitumor immune response. In the Si9GM treatment group, the proportion of $CD4^+CD25^+Foxp3^+$ Tregs in the spleen was significantly diminished. When this therapy was combined with anti-PD-1 treatment, the proportion of Tregs further decreased (**Figure 4, right**).

Expression characteristics and cold-to-hot transformation potential of the cGAS–STING pathway among tumor types

The cGAS–STING pathway notably shows context-dependent tumor immune regulation. Its activity status is closely associated with the "cold" or "hot" immune phenotype of tumors and profoundly influences the response to immunotherapy. In certain tumor types, this pathway may be suppressed, thus leading to a "cold" immune phenotype, or may be effectively activated, thus driving the infiltration of immune cells such as T cells to form a "hot" TME. Therefore, cGAS–STING activation does not universally lead to effective antitumor immunity across all cancer types. Appropriate activation of this pathway exerts critical antitumor efficacy primarily within "cold" tumors. More critically, appropriately activating the suppressed cGAS–STING pathway through specific interventions can effectively achieve transformation from a "cold" to a "hot" immune phenotype, thereby providing a key target for improving sensitivity to immunotherapy.

Breast cancer

In BC, the function of the cGAS–STING pathway is spatiotemporally dependent. Acute activation induces antitumor immunity, whereas chronic activation, such as that induced by CIN, shifts toward NF-κB and promotes IL-6/STAT3 signaling, which in turn facilitates cancer cell survival and promotes an immunosuppressive microenvironment[115,116].

A critical clinical driver of this acute activation is radiotherapy, which substantially relies on the cGAS–STING axis to modulate BC immunogenicity. Groundbreaking work by Demaria and colleagues[117] has established that radiation-induced antitumor immunity is governed by a strict dose-dependent threshold dictated by the DNA exonuclease three prime repair exonuclease 1 (TREX1). Radiation induces DNA damage and leads to the accumulation of cytosolic dsDNA. Subsequently, activation of the cGAS–STING pathway triggers IFN-I secretion and leads to recruitment of basic leucine zipper ATF-like transcription factor 3 (BATF3)-dependent DCs, which prime $CD8^+$ T cells. However, when the radiation dose per fraction exceeds 12–18 Gy in BC models, TREX1 is markedly upregulated. This exonuclease rapidly degrades the immunogenic cytosolic dsDNA, and consequently abrogates cGAS–STING activation and the abscopal effect otherwise achieved with ICIs. In contrast, fractionated radiotherapy regimens below this threshold, such as 8 Gy per fraction for three fractions, evade TREX1 induction. This fractionated approach successfully amplifies cGAS–STING signaling and enhances systemic tumor clearance[117,118].

Beyond radiation, targeted pharmacological strategies are being developed to exploit this pathway. Ka et al.[119] have proposed that nuclear receptor subfamily 1 group D member 1 (NR1D1) agonists might provide a potential therapeutic strategy for converting "cold" tumors to "hot" ones in BC models. Deficiency in the nuclear receptor NR1D1 led to attenuated cGAS–STING signaling, decreased infiltration of $CD8^+$ T cells and NK cells, and the formation of an immune-excluded "cold" TME. In contrast, NR1D1 agonists activated cGAS–STING, increased the infiltration of $CD8^+$ T cells and NK cells, and transformed the TME into a "hot," immune-infiltrated state (**Figure 5A**). Beyond these preclinical explorations, the STING agonist XMT-2056 was evaluated in a phase I clinical trial (NCT05514717) for advanced solid tumors, including BC, as a potential targeted strategy to drive the cold-to-hot tumor transition in clinical practice.

Glioblastoma (GBM)

In GBM, the cGAS–STING pathway is often functionally suppressed because of epigenetic silencing. Although this suppression might not directly dictate intrinsic tumor immunogenicity, it deprives the microenvironment of critical innate immune adjuvant signals. In contrast, when engaged, for example, by DNA or CDNs released from dying tumor cells after chemotherapy or radiotherapy, STING activation induces IFN-I signaling essential for APCs, upregulates costimulatory ligands, and promotes release of chemokines such as CXCL9 and CXCL10 that facilitate T-cell trafficking to tumor sites. *STING1* is frequently subject to epigenetic silencing in GBM, thus contributing to the tumor's inherently low immunogenic baseline and maintaining the typical immunologically "cold" phenotype[120].

von Roemeling et al.[121] have reported that combining CD47 blockade with temozolomide induces ER stress and calreticulin translocation in tumor cells, and consequently increases their phagocytic clearance. Subsequent activation of the cGAS–STING pathway and promotion of antigen cross-presentation and IFN-I production ultimately lead to a substantial increase in $CD8^+$ T-cell priming and infiltration, and effectively inhibit tumor growth. Similarly, exploiting specific epigenetic vulnerabilities, such as protein phosphatase 2A (PP2A) catalytic subunit deficiency, provides a potent intrinsic strategy to reverse immune exclusion in GBM by creating intracellular stress that intrinsically rewires the local microenvironment. Specifically, increased infiltration of $CD8^+$ T cells, NK cells, and DCs, and decreases in immunosuppressive macrophages, enhances tumor sensitivity to immune checkpoint blockade and radiotherapy[122] (**Figure 5B**).

These mechanisms, by collectively promoting immune cell infiltration and the formation of an immunologically "hot"

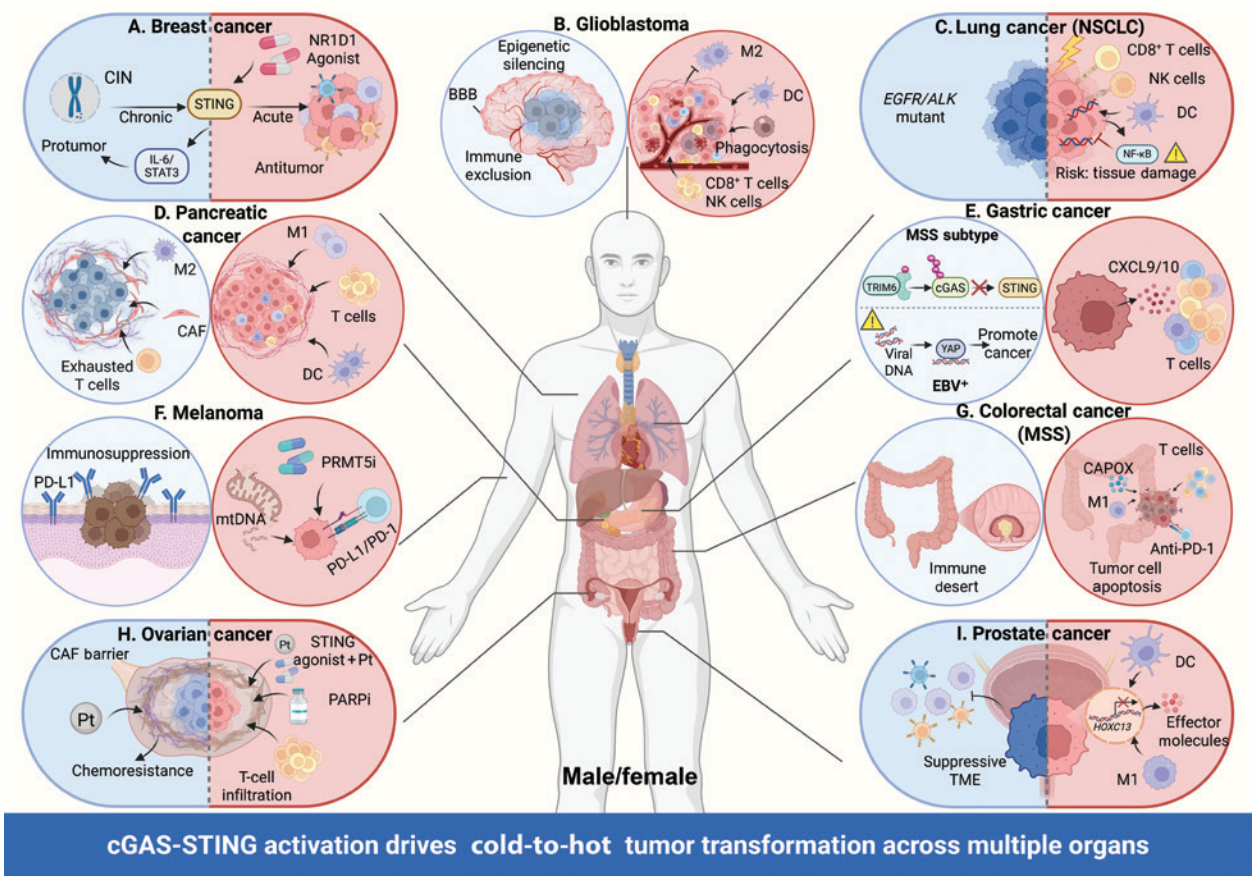


Figure 5 The cGAS–STING pathway drives cold-to-hot immune phenotype transformation across multiple organs. (The transition from blue to red in the figure represents cGAS–STING pathway activation.) This figure systematically illustrates the heterogeneous activation patterns of the cGAS–STING pathway and its potential to remodel the TME across various anatomical sites. Despite distinct baseline immune landscapes, targeted activation of cGAS–STING signaling can convert immunosuppressive "cold" tumors into "hot" phenotypes. (A) Breast cancer: A temporal dependency is highlighted, in which chronic activation driven by CIN promotes tumorigenesis *via* IL-6/STAT3, whereas acute activation induced by NR1D1 agonists drives antitumor immune inflammation. (B) Glioblastoma: To overcome immune exclusion caused by epigenetic silencing, activation of cGAS–STING signaling enhances phagocytosis, decreases M2 macrophages, and promotes the infiltration of $CD8^+$ T cells, DCs, and NK cells. (C) Lung cancer: In *EGFR/ALK*-mutant NSCLC, pathway activation may promote the recruitment of immune cells; however, sustained NF-κB-mediated inflammation poses a risk of tissue damage. (D) Pancreatic cancer: Targeting *ANXA1* or *TP53BP1* activates the pathway, thus overcoming fibrotic barriers, and increasing the populations of M1 macrophages, DCs, and effector T cells. (E) Gastric cancer: This cancer exhibits significant molecular subtype-dependent differences. In MSS subtypes, TRIM6 suppresses cGAS *via* ubiquitination and consequently maintains a cold phenotype; in contrast, in EBV-positive subtypes, viral DNA-induced activation paradoxically promotes tumor progression *via* the YAP pathway. After activation, the pathway effectively recruits $CD8^+$ T cells by inducing the production of T-cell chemoattractants such as CXCL9/10. (F) Melanoma: PRMT5i or mtDNA leakage triggers chemokine secretion and significantly enhances therapeutic efficacy in combination treatment with ICIs. (G) Colorectal cancer: In immune-desert MSS colorectal cancer, CAPOX chemotherapy regimens activate the cGAS–STING pathway and act synergistically with anti-PD-1 therapy in triggering immunogenic cell death and promoting M1 macrophage polarization. (H) Ovarian cancer: To overcome chemotherapy resistance and CAF barriers, the use of PARPi or STING agonists combined with Pt enhances T-cell infiltration. (I) Prostate cancer: Silencing of *HOXC13* expression relieves cGAS–STING inhibition, reverses the suppressive microenvironment, and may promote immune-cell recruitment and myeloid remodeling. ALK, anaplastic lymphoma kinase; ANXA1, annexin A1; BBB, blood–brain barrier; CAF, cancer-associated fibroblast; CAPOX, capecitabine and oxaliplatin; CD, cluster of differentiation; cGAS, cyclic GMP-AMP synthase; CIN, chromosomal instability; CXCL9/10, C-X-C motif chemokine ligand 9/10; DC, dendritic cell; EBV, Epstein–Barr virus; EGFR, epidermal growth factor receptor; HOXC13, homeobox C13; ICI, immune checkpoint inhibitor; IL-6, interleukin 6; M1/M2, macrophage phenotypes; MSS, microsatellite stable; mtDNA, mitochondrial DNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer cell; NR1D1, nuclear receptor subfamily 1 group D member 1; NSCLC, non-small cell lung cancer;

PARPi, poly(ADP-ribose) polymerase inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PRMT5i, protein arginine methyltransferase 5 inhibitor; Pt, platinum-based chemotherapy; STAT3, signal transducer and activator of transcription 3; STING, stimulator of interferon genes; TME, tumor microenvironment; TP53BP1, tumor protein p53 binding protein 1; TRIM6, tripartite motif containing 6; YAP, Yes-associated protein. (Figure created with BioRender, www.biorender.com.)

phenotype, provide novel strategies for increasing the sensitivity of GBM to immunotherapy.

Lung cancer

Lung cancer accounts for most cancer-related deaths worldwide, and non-small cell lung cancer (NSCLC) represents more than 85% of all lung cancer diagnoses[123,124]. In NSCLC, the cGAS–STING axis is a critical determinant of the therapeutic response to DNA damage. Radiotherapy and chemotherapy activate this pathway, and consequently may help overcome the immunosuppressive phenotype of resistant subsets with *EGFR* or *ALK* mutations[125-127]. Furthermore, Yang et al.[128] summarized evidence that STING activation promotes DC maturation and T-cell infiltration; when combined with PD-1/PD-L1 inhibitors, this immune remodeling effectively induces tumor rejection.

However, STING activation in NSCLC presents a notable clinical duality. Excessive activation triggers NF-κB-mediated inflammation and contributes to radiation-induced lung injury (**Figure 5C**). Therefore, optimizing the spatiotemporal window of STING activation is essential to maximize tumor immunogenicity while sparing healthy lung parenchyma. This synergy has been a focus of clinical exploration. For example, a recent phase II trial (NCT05846646[129]) has investigated the combination of intratumoral IMSA101 with personalized ultra-fractionated stereotactic adaptive radiotherapy (PULSAR) and ICIs in oligometastatic NSCLC.

Beyond NSCLC, small cell lung cancer (SCLC) poses a distinct microenvironmental challenge driven by extensive epigenetic silencing. SCLC remains notoriously recalcitrant to immunotherapy, because of intrinsic downregulation of MHC class I molecules and innate immune sensors. Mahadevan et al.[130] have demonstrated that enhancer of zeste homolog 2 (EZH2) inhibition effectively derepresses the cGAS–STING axis and restores antigen presentation. This targeted epigenetic rewiring creates a critical therapeutic vulnerability allowing subsequent STING agonism to effectively prime antigen-specific CTLs and sensitize these highly aggressive tumors to immune checkpoint blockade.

Pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC), a quintessential "cold" tumor, is characterized by a dense desmoplastic stroma and a highly immunosuppressive myeloid compartment in which innate sensing is typically silenced. Overcoming this barrier requires context-specific pathway uncoupling. Hou et al.[131] have reported that high expression of annexin A1 (ANXA1) correlates with poor prognosis by maintaining this suppressive state. Targeted deletion of *ANXA1* specifically restrains macrophage efferocytosis and leads to accumulation of undigested cytoplasmic DNA. Subsequently, local triggering of the STING pathway within the myeloid compartment effectively shifts the microenvironmental balance, by promoting M1 macrophage polarization and effector T-cell enrichment while depleting exhausted T cells and M2 macrophages, thereby breaching the PDAC immune barrier. Similarly, exploiting specific genetic vulnerabilities, such as *TP53BP1* loss or CD73 inhibition, creates unique intracellular stress signatures that unleash STING signaling, which strongly correlates with improved ICI responsiveness[132,133] (**Figure 5D**).

Gastric cancer

In gastric cancer, the status of the cGAS–STING pathway is strongly correlated with molecular subtypes. In the deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) subtype, the intrinsic expression of cGAS–STING in tumor cells is substantially elevated. This activation effectively recruits $CD8^+$ T cells by inducing the production of T-cell chemoattractants such as CXCL9, CXCL10, CXCL11 and CCL5, thereby fostering a "hot" TME characterized by high immune cell infiltration. This robust inflammatory baseline provides a crucial biological rationale for the enhanced sensitivity to immunotherapy frequently observed in this subtype, although clinical responses remain heterogeneous across patients[83]. Further research by Niu et al.[134] has revealed that in microsatellite stable (MSS)-type gastric cancer, the cGAS–STING pathway is suppressed by tripartite motif containing 6 (TRIM6) *via* the ubiquitin–proteasome pathway. Activation of the cGAS–STING pathway in this context converts MSS-type gastric cancer from an immunologically "cold" state to a "hot" state and reverses resistance to ICIs. Notably, Wen et al.[70] have demonstrated that in EBV-positive gastric cancer, viral DNA activates the cGAS–STING pathway, which in turn induces OLFM4 expression and promotes YAP signaling; therefore, these findings have revealed a protumorigenic role of this pathway in this specific cancer type (**Figure 5E**).

In summary, the effect of the cGAS–STING pathway in gastric cancer is highly dependent on the molecular subtype context. Its activation plays an immunostimulatory role in the dMMR/MSI-H or MSS subtype, whereas in EBV-associated gastric carcinoma, this pathway might be co-opted to promote tumor progression. This differential regulation substantially influences tumor immunogenicity and therapy response.

Melanoma

ICI therapy has demonstrated significant clinical efficacy in immunologically infiltrated tumors such as melanoma[135]. In these inherently "hot" tumors, the therapeutic focus shifts from initial immune recruitment to sustaining effector function and overcoming acquired resistance. Various targeted interventions, including protein arginine methyltransferase 5 (PRMT5) inhibition[136] or specific chemotherapeutic regimens[137], have been reported to enhance inflammatory signaling related to DNA/mitochondrial DNA (mtDNA) sensing in melanoma (**Figure 5F**). Notably, whereas chronic STING activation may induce immunosuppression *via* upregulation of PD-L1 expression, short-term activation can act synergistically with ICIs and substantially increase therapeutic efficacy[82].

Colorectal cancer

CRC is categorized primarily into two subtypes by DNA mismatch repair (MMR) status: the dMMR/MSI-H subtype and the DNA MMR-proficient/microsatellite stable (pMMR/MSS) subtype[138]. Patients with CRC with different microsatellite statuses exhibit distinct compositions and distributions of immune cells and cytokines within the TME[139]. In dMMR/MSI-H CRC, the accumulation of cytoplasmic DNA effectively activates the cGAS–STING pathway, and consequently drives IFN-I secretion and $CD8^+$ T-cell infiltration. Subsequently, an immune-infiltrated TME is created, and the response to anti-PD-1 therapy is significantly enhanced[140-142], thus resulting in the classification of these tumors as "hot." However, the persistent intrinsic resistance in a subset of these patients underscores the complexity of translating a "hot" phenotype into consistent clinical benefit. In contrast, the TME in most MSS CRCs typically presents an immune-excluded or immune-desert phenotype and is considered a "cold" tumor[139]. For MSS CRC, even when chemotherapy is combined with ICIs, clinical responses remain limited[141]. Therefore, a key research direction is developing strategies to convert "cold" MSS CRC tumors into "hot" tumors. This conversion is aimed at enhancing chemosensitivity, inducing immunogenicity, and ultimately increasing responsiveness to immunotherapy.

Park et al.[143] have developed an oral capecitabine and oxaliplatin (CAPOX) nanoparticle regimen for treating CRC. By inducing synergistic DNA damage, this regimen activates the cGAS–STING pathway, triggers immunogenic cell death, and promotes M1 macrophage polarization, thereby successfully converting cold tumors into hot tumors (**Figure 5G**). *In vivo* experiments manifested that this regimen, when combined with anti-PD-1, achieved complete tumor resolution in 91% of mice bearing syngeneic CT26 subcutaneous tumors. Another study by Zhu et al.[144] has described an epigenetic gene involved in DNA damage repair, PRMT5. Its inhibition enhanced sensitivity to irinotecan and cooperatively induced an MMR-deficient-like state characterized by a deficiency in the MMR protein Postmeiotic segregation increased 2 (PMS2). Subsequent release of cytosolic dsDNA activated the cGAS–STING pathway, thereby augmenting antitumor immunotherapy through a DC- and T-cell-dependent mechanism.

Ovarian cancer (OC)

Although immune cell infiltration can be observed in some cases of OC, most cases are classified as "immune-excluded" or "immune-desert" types, in which immune cells are confined to the tumor stroma or are almost entirely absent[145]. OC is therefore generally considered a "cold" tumor[146]. Platinum-based chemotherapy induces the release of DNA from cancer cells into CAFs, thus activating the cGAS–STING pathway in the latter. However, this response might contribute to chemotherapy resistance in cancer cells[147]. STING agonists offer a new direction for combination therapy in OC. Ghaffari et al.[148] have demonstrated that combining a STING agonist with platinum-based chemotherapy enhances T-cell infiltration, prolongs survival in a mouse model of serous OC, decreases ascites formation, and improves overall condition in mice[149]. Another study has indicated that poly(ADP-ribose) polymerase inhibitors activate an antitumor immune response through a STING-dependent mechanism and consequently enhance the efficacy of PD-L1 inhibitors in an ID8 syngeneic mouse model[150] (**Figure 5H**).

Prostate cancer

Prostate cancer is notoriously inert to immunotherapy, because of a rigid, immunosuppressive TME lacking baseline T-cell infiltration[151]. In this context, driving the cold-to-hot transition relies on dismantling specific transcriptional repressors. Li et al.[152] have elucidated a critical regulatory axis involving homeobox C13 (HOXC13), an oncogenic homeobox transcription factor frequently overexpressed in prostate cancer. Silencing *HOXC13* directly alleviates suppression of the cGAS–STING pathway and triggers a targeted chemokine cascade. This targeted transcriptional rewiring effectively remodels the local microenvironment, potentially reducing the suppressive myeloid milieu and promoting immune-cell recruitment[153] (**Figure 5I**).

In summary, the cGAS–STING pathway is a central hub regulating the "cold" and "hot" phenotypes of the tumor immune microenvironment. In typical "cold" tumors, such as pancreatic cancer, GBM, and MSS CRC, this pathway is often functionally suppressed through various mechanisms, thus leading to insufficient T-cell infiltration and immune resistance. In contrast, in "hot" tumors, such as dMMR/MSI-H CRC and gastric cancer, the pathway is effectively activated by intrinsic tumor DNA damage signals, thus driving the production of IFN-I and T-cell chemoattractants, and consequently promoting immune cell infiltration. Targeted activation of the cGAS–STING pathway in the TME effectively converts "cold" tumors into "hot" tumors characterized by increased

infiltration of $CD8^+$ T cells, NK cells, and DCs, as well as decreased immunosuppression, thus markedly enhancing sensitivity to therapies such as ICIs. Therefore, targeting the cGAS–STING pathway to induce transition from a "cold" to "hot" tumor status is a key strategy for improving responses to immunotherapy.

Therapeutic strategies targeting the cGAS–STING pathway

Translational barriers and delivery strategies for STING agonists

The immunostimulatory potential of the cGAS–STING pathway renders it an attractive pharmacological target, because its activation within the TME induces effective cross-priming of tumor-specific antigens and promotes the infiltration of effector T cells[15]. Although first-generation STING agonists, primarily CDNs, have demonstrated promising efficacy in preclinical studies[154], their clinical translation and application have been substantially hindered by the operational limitations of intratumoral administration and the toxicity challenges associated with systemic delivery[15]. The current clinical landscape and research progress in representative cGAS–STING agonists are summarized in **Table 1**.

These toxicity challenges constitute a complex landscape of safety concerns and adverse events, which markedly narrow the therapeutic window. Potent and uncontrolled STING activation can trigger severe cytokine release syndrome[170,171], hepatotoxicity (elevated transaminases), and dose-limiting hematological toxicities, such as lymphopenia and thrombocytopenia. Notably, because the severity and nature of the toxicity profiles considerably vary among agonist molecules and delivery platforms, precise spatial and pharmacokinetic control are urgently needed.

To mitigate systemic toxicity and increase cytosolic delivery efficiency[172], early clinical trials relied primarily on the intratumoral injection of first-generation CDNs, such as ADU-S100 (NCT03937141[155] and NCT03172936[156]), MK-1454 (NCT03010176[158]), and E7766 (NCT04144140[160]). Although injection bypasses systemic toxicity, it has limited utility for deep-seated or widely metastatic lesions[173]. Subsequently, second-generation small-molecule agonists were developed for systemic intravenous (IV) administration, as exemplified by SNX281 (NCT04609579[163]) and SB 11285 (NCT04096638[164]). However, achieving an optimal balance between toxicity and efficacy remained a formidable challenge, many of these trials were ultimately terminated.

The suboptimal clinical efficacy observed in current trials can be attributed to several intrinsic factors:

1. Discrepancies in TME models: Most preclinical data on STING agonists rely on mouse syngeneic subcutaneous tumor models. However, these models are often oversimplified and lack the dense desmoplastic stroma and complex spatial architecture characteristic of human solid tumors, such as CRC[174]. In clinical practice, this robust physical barrier within the human TME severely restricts the effective penetration of free STING agonists into deep tumor regions, thereby inevitably hindering effector T-cell infiltration and the comprehensive activation of antitumor immunity[175].
2. Pharmacokinetic and delivery hurdles: Although intratumoral injection has demonstrated significant efficacy in superficial mouse models, performing serial injections into deep-seated visceral tumors or widely disseminated metastatic lesions is clinically unfeasible[176,177]. In contrast, systemic IV administration faces pharmacokinetic flaws, such as rapid renal clearance, and risks the indiscriminate activation of STING signaling in vascular endothelial cells and peripheral immune cells. A severe systemic inflammatory response is often triggered before the drug can accumulate at therapeutic concentrations within the TME[178,179]. Furthermore, insufficient dosing may inadvertently induce chronic, low-level STING signaling, which in turn triggers the aforementioned immunosuppressive feedback loops.
3. Paradoxical T-cell cytotoxicity: Sustained or high-dose exposure to STING agonists disrupts calcium homeostasis in effector T cells and triggers severe ER stress and subsequent apoptosis, thereby counteracting or even reversing the intended antitumor therapeutic effects[102,179].
4. ENPP1-mediated degradation: Human tumors frequently have upregulated expression of ENPP1. This phosphodiesterase rapidly hydrolyzes cGAMP and other natural CDNs in the extracellular space, thereby effectively neutralizing the agonists before they can reach and bind intracellular STING targets[38].
5. Species discrepancies and human STING polymorphism: The first-generation mouse STING agonist DMXAA demonstrated striking efficacy in mouse models[154] but completely failed in human clinical trials because it is structurally incapable of binding the human STING receptor[180]. Additionally, the human *TMEM173* gene[181], which encodes STING, exhibits significant allelic variation. Whereas *R232* is the predominant wild-type allele, a substantial proportion of the human population carries functional polymorphisms, such as the *HAQ*[182], *REF/H232*[183], or *AQ*[184] variants. These variants exhibit distinct conformational requirements and ligand-binding affinities. Consequently, STING agonists optimized solely for the wild-type receptor might fail to activate the pathway in patients with specific genetic variants[185].

To overcome these bottlenecks, current research is focused on multiple strategies. First, the rational design of novel STING agonists with improved physicochemical and pharmacokinetic properties, such as non-nucleotide small molecules, is aimed at enabling safe and effective systemic administration[186]. Second, the development of advanced

Table 1 Summary of representative STING agonists and their clinical development landscape

Category	Subclass/ characteristics	Representative agent	Tumor type	Administration route	Treatment regimen	Development stage	Status	Clinical trial code	Clinical results/reasons for termination
STING agonists	First generation: CDN analogs (based on natural or modified CDNs)	ADU-S100 (MIW815)	Head and neck cancer	IT	MIW815 + pembrolizumab	Phase II	Terminated	NCT03937141	Lack of substantial antitumor activity[155]
			Advanced solid tumors or lymphoma	IT	Monotherapy or in combination with spartalizumab	Phase I	Terminated	NCT03172936	Sponsor decision; limited antitumor activity[156]
			Advanced/metastatic solid tumors or lymphomas	IT	MIW815 + ipilimumab	Phase I	Terminated	NCT02675439	No substantial antitumor activity observed[157]
		MK-1454	Advanced solid tumors or lymphomas	IT	Monotherapy or in combination with pembrolizumab	Phase I	Completed	NCT03010176	Manageable safety and target engagement; preliminary efficacy in combination therapy[158]
			Recurrent head and neck squamous cell carcinoma	IT	MK-1454 + pembrolizumab	Phase II	Completed	NCT04220866	Manageable safety and modest combination efficacy in a small cohort[158]
		GSK3745417	Advanced solid tumors	IV	Monotherapy or in combination with dostarlimab	Phase I	Active, not recruiting	NCT03843359	Results posted; study remains active
			Hematologic malignancies	IV	Monotherapy	Phase I	Terminated	NCT05424380	Terminated because of sponsor's strategic portfolio reprioritization[159]
		E7766	Advanced solid tumors or lymphomas	IT	Monotherapy	Phase I	Terminated	NCT04144140	Terminated because of a corporate business decision[160]
			Non-muscle invasive bladder cancer	Intravesical	Monotherapy	Phase I	Withdrawn	NCT04109092	Withdrawn before patient enrollment because of a corporate business decision

Table 1 Continued

Category	Subclass/ characteristics	Representative agent	Tumor type	Administration route	Treatment regimen	Development stage	Status	Clinical trial code	Clinical results/reasons for termination
		MK-2118	Advanced solid tumors	IT or SC	Monotherapy or in combination with pembrolizumab	Phase I	Terminated	NCT03249792	Terminated for business reasons; limited antitumor activity[161]
		BMS-986301	Advanced solid tumors	IM and IT and IV	Monotherapy and combination therapy with nivolumab and ipilimumab	Phase I	Completed	NCT03956680	Data pending publication
		IMSA101	Advanced solid tumors	IT	Monotherapy or in combination with an immune checkpoint inhibitor	Phase I/IIA	Completed	NCT04020185	Manageable safety but minimal antitumor activity[162]
			Metastatic kidney cancer (SPARK)	IT	PULSAR in combination with IMSA101 and nivolumab	Phase II	Recruiting	NCT06601296	Results pending
			Oligoprogressive solid tumor malignancies	IT	PULSAR + pembrolizumab or nivolumab administered with or without IMSA101	Phase II	Terminated	NCT05846659	Terminated because of corporate strategy change[129]
			Oligometastatic NSCLC and RCC	IT	PULSAR + pembrolizumab or nivolumab administered with or without IMSA101	Phase II	Terminated	NCT05846646	Terminated because of corporate strategy change[129]
	Second generation: non-nucleotide small molecules (systemic delivery optimized)	SNX281	Advanced solid tumors or lymphomas	IV	Monotherapy or in combination with pembrolizumab	Phase I	Terminated	NCT04609579	Terminated because of sponsor decision (unrelated to safety)[163]
		SB 11285	Advanced solid tumors	IV	Monotherapy or in combination with atezolizumab	Phase I	Completed	NCT04096638	Manageable safety profile but insufficient clinical activity for further progression[164]

Table 1 Continued

Category	Subclass/ characteristics	Representative agent	Tumor type	Administration route	Treatment regimen	Development stage	Status	Clinical trial code	Clinical results/reasons for termination
		Dazostinag (TAK-676)	Advanced or metastatic solid tumors	IV	Monotherapy or in combination with pembrolizumab	Phase I/II	Completed	NCT04420884	Limited preliminary antitumor activity[165]
			Advanced solid tumors	IV	Radiotherapy + pembrolizumab + TAK-676	Phase I	Completed	NCT04879849	Well tolerated but showed a modest response rate[166]
		BI 1387446	Advanced or metastatic solid tumors	IT	Monotherapy or in combination with ezabenlimab	Phase I	Completed	NCT04147234	Limited antitumor activity was observed[167]
		CRD3874-SI	Relapsed/refractory acute myeloid leukemia	IV	Monotherapy	Phase I	Suspended	NCT06626633	Company withdrew support and investigational product
			Solid tumors	IV	Monotherapy	Phase I	Recruiting	NCT06021626	Ongoing early-phase trial results pending
Nanotechnology and novel delivery	ADCs/ISACs	TAK-500	Advanced or metastatic solid tumors	IV	TAK-500 with or without pembrolizumab	Phase I/II	Terminated	NCT05070247	Terminated because of clinical futility[168]
		XMT-2056	Advanced/Recurrent solid tumors	IV	Monotherapy	Phase I	Terminated	NCT05514717	Development discontinued; no results posted
	Bacterial vector	SYNB1891	Advanced solid tumors and lymphoma	IT	Monotherapy or in combination with atezolizumab	Phase I	Terminated	NCT04167137	Terminated because of business reasons[169]
	Exosome based	exoSTING (CDK002)	Advanced/ metastatic, recurrent, injectable solid tumors	IT	Monotherapy	Phase I/II	Completed	NCT04592484	Demonstrated biomarker activation but development halted

Data were retrieved from ClinicalTrials.gov. Trial status was verified on July 29, 2026. ADC, antibody-drug conjugate; CDN, cyclic dinucleotide; IM, intramuscular; ISAC, immune-stimulating antibody conjugate; IT, intratumoral; IV, intravenous; NSCLC, non-small cell lung cancer; PULSAR, personalized ultra-fractionated stereotactic adaptive radiotherapy; RCC, renal cell carcinoma.

targeted delivery platforms is essential to ensure tumor-specific accumulation and circumvent premature degradation[38]. This strategy encompasses a broad spectrum of emerging technologies, including traditional nanotechnology (polymeric, liposomal, and inorganic platforms) using structural shielding to protect CDNs against enzymatic degradation[187] and exploit TME-responsive mechanisms for targeted intracellular release[179,188]; ISACs; ADCs; and bioengineered vectors[189]. These next-generation platforms offer distinct advantages: antibody-based conjugates (e.g., XMT-2056 and TAK-500) enable tumor- or myeloid-specific targeting and therefore decrease off-target toxicity[172,187] and T-cell apoptosis; bacterial vectors (e.g., SYNB1891)[169] leverage natural tropism for APC-targeted delivery; and exosome platforms (e.g., exoSTING)[190] protect CDNs against ENPP1-mediated degradation while avoiding bystander T-cell toxicity. These integrated strategies ensure potent, precise, and safe localized activation of the cGAS–STING cascade deep within the immunosuppressive microenvironment.

Immunotherapeutic combination strategies targeting the cGAS–STING pathway

Beyond optimizing agonists and their delivery, combining STING pathway agonists with other therapeutic modalities is being actively pursued to maximize clinical benefit. A key impetus for this combinatorial approach is its potential for more rapid clinical translation than what could be achieved with the development of novel compounds or complex delivery systems.

Strategies combining the cGAS–STING pathway and immune checkpoint inhibitors

ICIs target primarily cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), PD-1, and its primary ligand PD-L1[191]. These agents have been approved for standard clinical treatment in numerous cancers; however, their overall response rates and efficacy remain suboptimal. ICIs exhibit varying activity across cancer types. Noninflammatory tumors, including those with immune-excluded and immune-desert phenotypes, are typically insensitive to PD-1/PD-L1 inhibitor therapy[192]. Because ICI efficacy substantially relies on baseline tumor immunogenicity and T-cell infiltration[193], combining ICIs with cGAS–STING pathway activation is being actively investigated to drive the cold-to-hot phenotypic transition (**Figure 6A**). This combination strategy is aimed at sensitizing resistant tumors. However, achieving universal clinical outcomes remains challenging, because initial immune infiltration must overcome compensatory immunosuppressive feedback loops to prevent secondary resistance.

Sensitization to PD-1/PD-L1 blockade: Multiple preclinical models have indicated substantial synergy between STING activation and PD-1/PD-L1 inhibitors. For example, combining the STING agonist MSA-2 with the bispecific antibody YM101 fundamentally remodels the *in vivo* TME and substantially extends survival in immunologically "excluded" CT26 models[194]. Similarly, lipid nanoparticle-delivered STING agonists have successfully overcome PD-1 resistance in B16-F10 lung metastasis models by driving NK-cell-mediated PD-L1 upregulation on cancer cells[195]. Beyond exogenous agonists, targeted genetic interventions such as *PTPRT* deletion sensitize resistant NSCLC to anti-PD-1 therapy in a strictly STING-dependent manner[196]. Exploiting specific metabolic vulnerabilities, such as inhibiting the depalmitoylase lysophospholipase like 1 (LYPLAL1), in combination with PD-1 inhibitors, similarly restores antigen presentation and translates directly into prolonged overall survival[197].

Synergy with dual checkpoint blockade: To overcome deeper immune tolerance, STING activation is increasingly being combined with dual ICI regimens. In a spontaneous PDAC KPC mouse model, Li et al.[198] have demonstrated that although dual blockade (anti-PD-1 plus anti-CTLA-4) alone does not improve outcomes, the addition of an intramuscular STING agonist significantly prolongs survival. This robust synergistic effect underscores the need for innate immune licensing to fully unleash the potential of dual adaptive checkpoint blockade, thus providing a rationale for clinical evaluation (e.g., NCT03956680[198]).

Strategies combining the cGAS–STING pathway and adoptive cell immunotherapy

Adoptive cell transfer therapy (ACT) involves the isolation of natural host T cells with antitumor activity from either the patient or a donor and the infusion of these cells into tumor-bearing patients to stimulate and expand antigen-specific T-cell immunity[199]. Multiple lines of evidence indicate that the host immune microenvironment significantly influences the efficacy of ACT[200]. Targeted cGAS–STING activation offers a powerful preconditioning mechanism to remodel these "cold" niches, thereby synergistically enhancing the *in vivo* efficacy of diverse ACT modalities (**Figure 6B**).

The limited solid tumor penetration and poor persistence of chimeric antigen receptor (CAR) T cells can be successfully reversed *via* STING signaling[201]. Co-administration of STING agonists, such as DMXAA or nanoparticle-delivered cGAMP, substantially improves the tumor trafficking and survival of CAR-T cells[201,202]. Furthermore, targeted pharmacological preconditioning has successfully overcome physical and biochemical barriers. For example, the flap endonuclease 1 (FEN1) inhibitor SC13, by exploiting specific DNA repair defects, triggers robust intrinsic STING signaling, thus directly amplifying CAR-T-cell killing efficiency and driving the parenchymal infiltration of supportive host $CD8^+$ T cells in OC[203]. Alternatively, to entirely circumvent the potential T-cell toxicity of high-dose STING agonists, researchers have engineered CAR-NK cells. By leveraging STING agonists to inflame the TME while adoptively transferring naturally STING-resistant CAR-NK cells, this approach establishes a

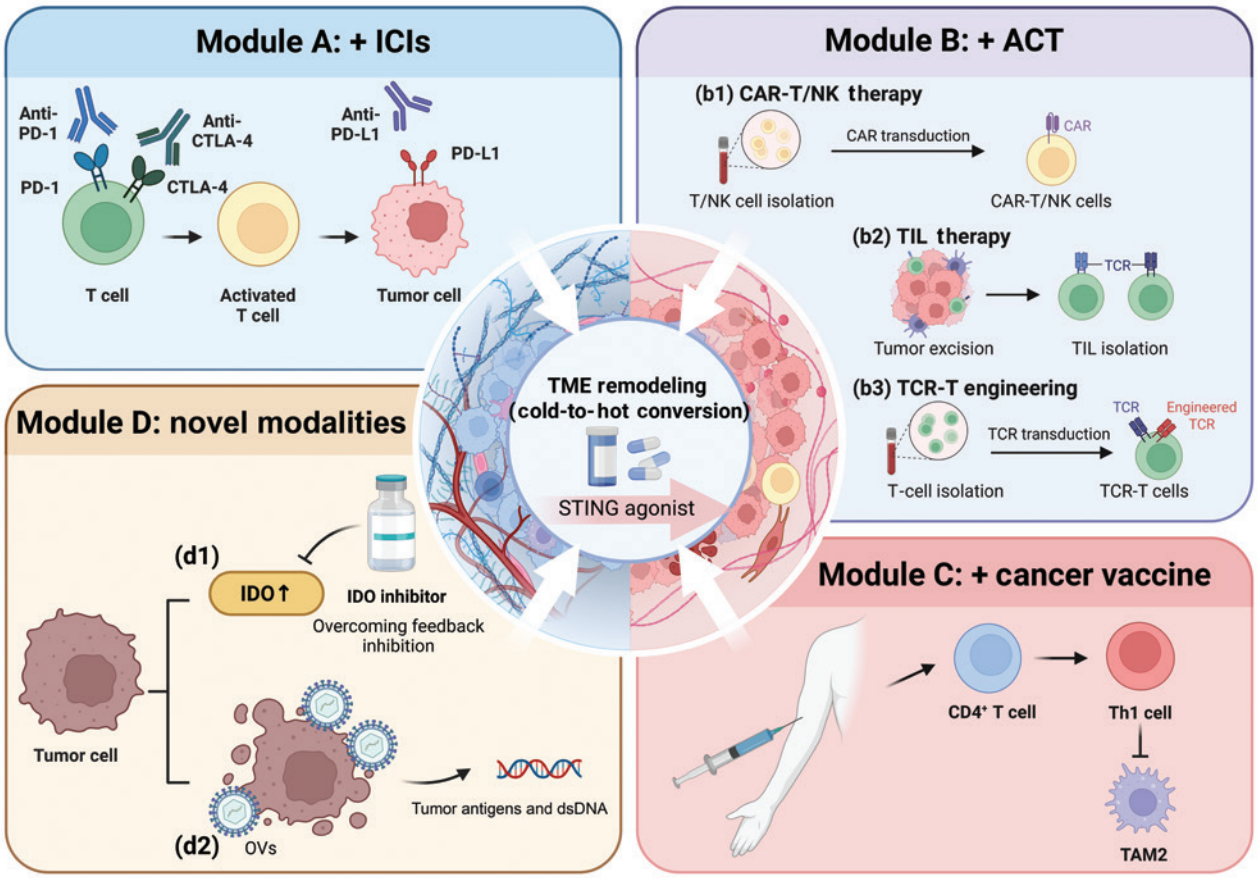


Figure 6 Combinatorial immunotherapeutic strategies targeting the cGAS–STING pathway. This figure illustrates four primary combination modalities centered on STING agonists, aimed at remodeling the TME to achieve a transformation from an immunosuppressive "cold" phenotype to an immunoreactive "hot" phenotype. (A) Combination with ICIs: STING agonists act synergistically with anti-PD-1/PD-L1 and anti-CTLA-4: cGAS–STING pathway activation enhances tumor immunogenicity and promotes the infiltration and activation of effector T cells, thereby overcoming the primary resistance of "cold" tumors to ICIs and demonstrating synergistic antitumor effects in preclinical models. (B) Combination with ACT: This strategy leverages the *ex vivo* engineering of immune cells for precise tumor targeting. Specifically, in CAR-T/NK cell therapy, the process begins with T/NK cell isolation from a patient or allogeneic donor's blood, followed by the transduction of a CAR to generate engineered T/NK cells (b1). TIL therapy involves excising tumor tissue from the patient, followed by the isolation of TILs for expansion and reinfusion (b2). Furthermore, TCR-T engineering involves T-cell isolation and genetic modification to produce TCR-T cells targeting a known antigen (b3). (C) Combination with cancer vaccines: Acting as potent immune adjuvants, STING agonists induce $CD4^+$ T-cell polarization toward the Th1 phenotype and decrease immunosuppressive TAM2s, thereby enhancing vaccine-induced specific immune responses. (D) Novel combination modalities: To address the negative feedback mechanism wherein STING activation induces upregulation of IDO activity, the co-administration of IDO inhibitors blocks this metabolic immunosuppressive circuit and consequently overcomes the limitations of monotherapy (d1); additionally, other novel synergistic strategies are highlighted, such as the co-administration of STING agonists and OVs to elicit durable immune memory (d2). ACT, adoptive cell therapy; CAR, chimeric antigen receptor; CD, cluster of differentiation; cGAS, cyclic GMP-AMP synthase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; dsDNA, double-stranded DNA; ICI, immune checkpoint inhibitor; IDO, indoleamine 2,3-dioxygenase; NK, natural killer cell; OVs, oncolytic viruses; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; STING, stimulator of interferon genes; TAM2, tumor-associated macrophage type 2; TCR, T-cell receptor; Th1, T helper cell type 1; TILs, tumor-infiltrating lymphocytes; TME, tumor microenvironment. (Figure created with BioRender, www.biorender.com.)

highly favorable immunogenic niche without compromising the viability of the infused effector cells[93].

Reinvigorating TILs: Beyond engineered cellular therapies, STING activation fundamentally supports the local expansion and antigen-recognition capabilities of endogenous TILs. Intratumoral administration of the STING agonist ADU-S100 significantly increases the clonal diversity and antigen-driven specific expansion of TILs[204]. At the epigenetic level, restoring suppressed STING expression with the DNA methylation inhibitor 5-aza-2′-deoxycytidine markedly upregulates MHC class I molecules on melanoma cells and fundamentally shapes tumor antigenicity, thus enhancing TIL-mediated cytotoxicity[205].

Potentiating T-cell receptor-engineered T cells (TCR-T): Similarly, targeted cGAS–STING activation offers a potent pharmacological preconditioning strategy for TCR-T cell therapies. Preconditioning TCR-T cells with STING agonists such as diABZI triggers intrinsic TBK1-IFN-γ signaling, thus dynamically enhancing their ability to eradicate low-antigen-expressing tumor cells *in vivo* without a need for additional complex genetic modifications[206].

Strategies combining the cGAS–STING pathway and cancer vaccines

Recent studies have indicated that STING agonists can serve as adjuvants for tumor vaccines and play a major role in antitumor therapy (**Figure 6C**). Rossi et al.[207] have reported that combining a STING agonist with a protein-based cancer vaccine by using the KISIMA platform synergistically remodels the TME, by converting "cold" tumors into "hot" tumors. This combination strategy resulted in a 2.5-fold increase in the intratumoral infiltration of $CD8^+$ T cells and non-Treg $CD4^+$ T cells, promoted the polarization of $CD4^+$ T cells toward a Th1 phenotype, concurrently decreased immunosuppressive M2-type TAMs, and ultimately reversed the immunosuppressive state. Beyond broad protein-based platforms, STING adjuvants can enable specific peptide vaccines to overcome genetically driven immunosuppression. Mota et al.[208] have demonstrated that combining an anaplastic lymphoma kinase (ALK)-targeted peptide vaccine with a STING adjuvant successfully restores the immunogenicity of inherently "cold" *ALK*-rearranged NSCLC. This tailored vaccination strategy robustly primes antigen-specific $CD8^+$ T cells and fundamentally dismantles the localized immune-excluded microenvironment.

Exploration of novel therapeutic modalities

As understanding of the TME deepens, novel combinatorial strategies are continually emerging to address specific therapeutic bottlenecks associated with STING activation.

Overcoming metabolic immunosuppression: STING pathway activation paradoxically upregulates the immunosuppressive enzyme IDO, thereby establishing a self-limiting negative feedback loop[209]. Co-administration of STING agonists with IDO inhibitors severs this metabolic circuit. In CRC, Shi et al.[210] have reported that this targeted dual-drug combination outperformed even a triple-drug regimen containing a PD-1 inhibitor. To further optimize delivery, Huang et al.[211] have engineered photoactivatable ER-targeting nanoparticles for the spatiotemporally controlled co-delivery of both agents. In BC models, this innovative nanotherapy successfully bypassed the aforementioned resistance mechanism, and achieved an 88% tumor inhibition rate by simultaneously triggering both systemic and localized immune responses.

Synergy with oncolytic virotherapy: Oncolytic viruses (OVs) can selectively lyse tumor cells and fundamentally remodel immunologically "cold" microenvironments[2,212]. Although STING-driven antiviral interferon responses theoretically restrict viral replication, this limitation is effectively bypassed in specific tumor models such as PDAC and squamous cell carcinoma, which inherently have functionally defective canonical STING signaling[213]. In these contexts, exogenous STING agonists act synergistically with OVs in eliciting deep, abscopal antitumor immunity, thereby establishing durable immune memory without hindering intrinsic viral replication. Expanding on this rationale, Mu et al.[214] have engineered a decomposable STING nanoagonist (OV-MnO_2/HE) to maximize the combinatorial synergy of Mn^{2+} and virotherapy (**Figure 6D**). This sophisticated nanomedicine overcomes local immunosuppression and directly translates into superior DC maturation rates, robust T-cell influx, and exceptional tumor growth suppression, while mitigating the toxicities associated with redundant systemic interventions.

Strategic mapping of STING modalities to distinct TME phenotypes

As indicated by the diverse combinatorial strategies detailed above, the successful application of STING agonists is highly dependent on the baseline state of the immune microenvironment. To circumvent the limitations of a "one-size-fits-all" treatment paradigm, and to bridge the conceptual gap between immunological classification and pharmacological intervention, specific STING-targeted modalities must be critically and explicitly mapped to distinct TME categories. On the basis of the aforementioned clinically actionable decision elements, we propose the following rationale-driven framework:

1. For the "immune-desert" phenotype: This phenotype is characterized by sparse TIL distribution and a lack of IFN gene signatures. The primary clinical hurdle is deficiency in initial antigen priming and effector T cells[215,216]. Consequently, actionable strategies must focus on *de novo* immune activation. This strategic goal directly aligns with the combination of STING agonists with cancer vaccines to provide specific tumor antigens, or with OVs to trigger immunogenic cell death, thereby facilitating a potent *in situ* vaccination effect[217].

2. For the "immune-excluded" phenotype: The core challenge is the physical sequestration of therapeutic agents and immune effector cells outside the tumor parenchyma. An optimal mapping strategy involves deploying nanotechnology-based targeted delivery systems to successfully penetrate the dense ECM. Concurrently, leveraging STING activation to drive vascular normalization[218] and CAF reprogramming[219] is crucial for actively dismantling these physical barriers and promoting T-cell infiltration.
3. For TMEs with heavy myeloid suppression: When the microenvironment is dominated by M2-type TAMs and MDSCs, precision targeting is required to reverse intense biochemical immunosuppression. Actionable strategies include using ADCs or ISACs to specifically deliver STING agonists to myeloid populations[220], thereby enforcing M2-to-M1 phenotypic polarization while avoiding off-target systemic toxicity. Additionally, combining STING agonists with IDO inhibitors can effectively antagonize concomitant metabolic immunosuppression[211].
4. For the "immune-inflamed" but exhausted phenotype: This phenotype features high spatial distribution of TILs that are functionally dysfunctional. In these "hot" tumors, intrinsic immune signals and T cells are present but impaired by compensatory inhibitory pathways. The mapping strategy here essentially focuses on immune reinvigoration, specifically, the combination of STING agonists with ICIs or ACT to restore and sustain the cytotoxic killing capability of the existing T-cell pool[221].

This tailored mapping approach ensures that the selected STING-targeted strategies actively dismantle the specific restrictive barriers of a given TME, thereby maximizing the likelihood of a successful cold-to-hot transition and achieving durable clinical benefit.

Summary and outlook

The cGAS–STING axis has fundamentally redefined the pharmacological landscape of tumor immunology, and it provides a potential switch for the cold-to-hot microenvironmental transition. However, the clinical translation of STING modulators currently faces a bottleneck due to the biological paradox of the pleiotropic and highly context-dependent nature of STING signaling. Whereas acute, targeted activation drives robust antigen cross-presentation and T-cell priming, chronic or off-target signaling inadvertently fuels an immunosuppressive cascade. This protumoral transition, driven by intrinsic CIN and metabolic checkpoints such as the IDO-kynurenine axis, ultimately facilitates immune evasion and tumor plasticity.

Pharmacologically, first-generation STING agonists are severely constrained by unfavorable pharmacokinetics, ubiquitous target expression across healthy tissues, and a notoriously narrow therapeutic index. Systemic administration frequently triggers generalized inflammation without achieving sufficient or sustained intratumoral exposure. Furthermore, the net therapeutic outcome of STING activation is not uniform but instead is intricately shaped by the interplay between the tumor's baseline microenvironment and the spatiotemporal dynamics of activation; therefore, empirical, non-stratified clinical applications are largely ineffective.

Overcoming these translational hurdles will require a definitive paradigm shift from blunt pathway agonism to precision spatiotemporal modulation. The development of next-generation therapeutics will increasingly focus on decoupling intratumoral efficacy from systemic toxicity through advanced delivery strategies and conditionally active platforms. More critically, future clinical trial designs must embrace a strategic mapping of distinct STING modalities to specific TME phenotypes. By deploying rational combination strategies, such as pairing STING agonists with IDO inhibitors for myeloid-suppressed microenvironments or with cancer vaccines for immune-desert states, and implementing biomarker-driven patient stratification, this highly complex pathway has potential to be successfully transformed into a cornerstone of next-generation precision immunotherapy.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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