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REVIEW

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Demystifying the cGAS-STING pathway: precision regulation in the tumor immune microenvironment

Qingyang Wang[1†], Yang Yu[2†], Jing Zhuang[3,4*], Ruijuan Liu[1,3*] and Changgang Sun[3,4*]

Abstract

The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway serves as an immune sentinel for cytosolic DNA, recognizing double-stranded DNA (dsDNA) derived from abnormally localized nuclear DNA or mitochondrial DNA (mtDNA), and plays a pivotal role in innate immune responses and tumor immune surveillance. Conventional antitumor therapies induce genomic instability and mitochondrial stress, leading to the release of nuclear DNA and mtDNA into the cytosol, thereby activating the cGAS-STING pathway. This activation triggers the production of type I interferons (IFN-I) and pro-inflammatory cytokines, which reshape the tumor immune microenvironment (TIME). However, the complexity of TIME reveals a "double-edged sword" effect of cGAS-STING signaling: while it activates antitumor immune responses, it also promotes immune escape and metastasis through the regulation of immunosuppressive cells and stromal components. This review comprehensively delineates the differential regulatory mechanisms of the pathway within TIME constituents, highlighting its multifaceted roles in tumor immunity. Furthermore, it reviews recent advances and challenges in targeting the cGAS-STING pathway for cancer immunotherapy, with the aim of advancing cGAS-STING signaling modulation as a key therapeutic strategy to reprogram TIME and overcome immunosuppression in antitumor treatment.

Keywords cGAS-STING pathway, Tumor immune microenvironment, Immune cells, Agonists, Combination therapy, "Double-edged sword" effect

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Introduction

The human immune system plays a pivotal role in tumor initiation, progression, and metastasis, serving as a cornerstone of cancer therapeutics. Through intricate biological networks, the immune system identifies and eliminates invading pathogens while maintaining organismal homeostasis, thereby establishing a robust defense against diseases. In mammalian immunity, evolution has endowed various pattern recognition receptors (PRRs) with the capacity to detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), enabling rapid initiation of host defense mechanisms [1]. Notably, aberrant RNA/DNA structures, RNA-DNA hybrids, and microbial-derived cyclic dinucleotides (CDNs) are classified as PAMPs. Immune cells engaged in innate immunity execute critical antitumor functions by recognizing distinct PAMPs through specific PRRs. In DNA sensing, cyclic GMP-AMP synthase (cGAS) stands out as a prominent PRR. Once cGAS binds to cytosolic double-stranded DNA (dsDNA), the cGAS-stimulator of interferon genes (STING) pathway is activated, triggering the production of type I interferon (IFN-I) and the secretion of inflammatory cytokines, ultimately eliciting potent innate immune responses [2].

With the paradigm shift in cancer research, the ecological characteristics of the tumor immune microenvironment (TIME) have become pivotal in deciphering mechanisms of therapeutic resistance [3]. TIME is a complex ecosystem composed of heterogeneous cellular populations (tumor cells, immune cells, stromal cells) and dynamically secreted factors, that not only drive immune evasion but also establish immunosuppressive niches through mechanisms such as metabolic reprogramming and aberrant angiogenesis. This understanding has redirected cancer therapeutic strategies from a sole focus on targeting malignant cells to systemically reprogramming the immunosuppressive microenvironment. Within TIME's intricate regulatory network, the cGAS-STING signaling pathway has garnered significant attention due to its dual regulatory effects on immune cell functions. Previous studies demonstrate that cGAS-STING signaling modulates the activation, infiltration, and phenotypic switching of immune cells, including macrophages and T cells [4]. Furthermore, synthetic cGAS-STING agonists can amplify T cell antitumor response programs to eliminate cancer cells in a precise and localized manner [5]. However, to fully harness the therapeutic potential of the cGAS-STING pathway in TIME, a deeper understanding of its regulatory mechanisms is imperative. Currently, critical knowledge gaps persist regarding the spatiotemporal specificity of cGAS-STING pathway regulation within TIME, limiting our ability to precisely modulate this pathway for optimal therapeutic outcomes. The activation threshold of this pathway is determined by spatiotemporal dynamics of microenvironmental factors such as DNA damage levels, mitochondrial genome stability, and micronuclei formation frequency, whose interplay dictates the activity and function of cGAS-STING signaling in specific TIME contexts [6]. Thus, unraveling these complex regulatory mechanisms is essential for developing more effective and safer therapeutics targeting the cGAS-STING pathway. In this review, we summarize the composition of TIME and its role in subverting immune surveillance, discusses existing and potential strategies for targeting TIME components, and focuses on redirecting cGAS-STING signaling to improve cancer immunotherapy, emphasizing its potential to overcome TIME-mediated immunosuppression.

cGAS-STING signaling pathway: a foundational overview

In 2013, the seminal work by Chen et al. identified cGAS in mammalian cells and revealed its ability to synthesize cyclic GMP-AMP (cGAMP), a second messenger that directly activates STING [7]. Since then, the cGAS-STING pathway has been implicated in diverse physiological and pathological processes [8]. In the context of cancer immunotherapy, cGAS-STING-derived signaling molecules coordinate with tumor cell-intrinsic IFN-I expression and chemokine secretion to establish an immunostimulatory tumor microenvironment [9, 10]. Here, this review provides an in-depth analysis of the structural features of the cGAS-STING pathway, its signal transduction mechanisms, and its critical functional roles within the TIME, aiming to elucidate its immense potential and broad therapeutic prospects in advancing cancer immunotherapy (Fig. 1).

Pathogens and cytoplasmic dsDNA induce conformational changes of cGAS

cGAS, a member of the nucleotidyltransferase (NTase) family, has an unstructured N-terminal domain and a C-terminal catalytic domain [11]. As a sensor for exogenous or pathogenic self-DNA in intracellular compartments, cGAS is activated via sequence-independent binding to dsDNA [12, 13]. This activation arises primarily from two pathological contexts: microbial invasion by DNA viruses, bacteria, or retroviruses that introduce exogenous DNA into the cytoplasm, and aberrant leakage of nuclear or mitochondrial self-DNA into the cytosol. Both scenarios disrupt cellular homeostasis, resulting in abnormal dsDNA accumulation that triggers cGAS activation [14, 15].

Advances in crystallographic and biochemical studies have elucidated the structural basis of dsDNA-cGAS binding and the molecular mechanisms underlying cGAS activation. The C-terminal NTase domain of cGAS

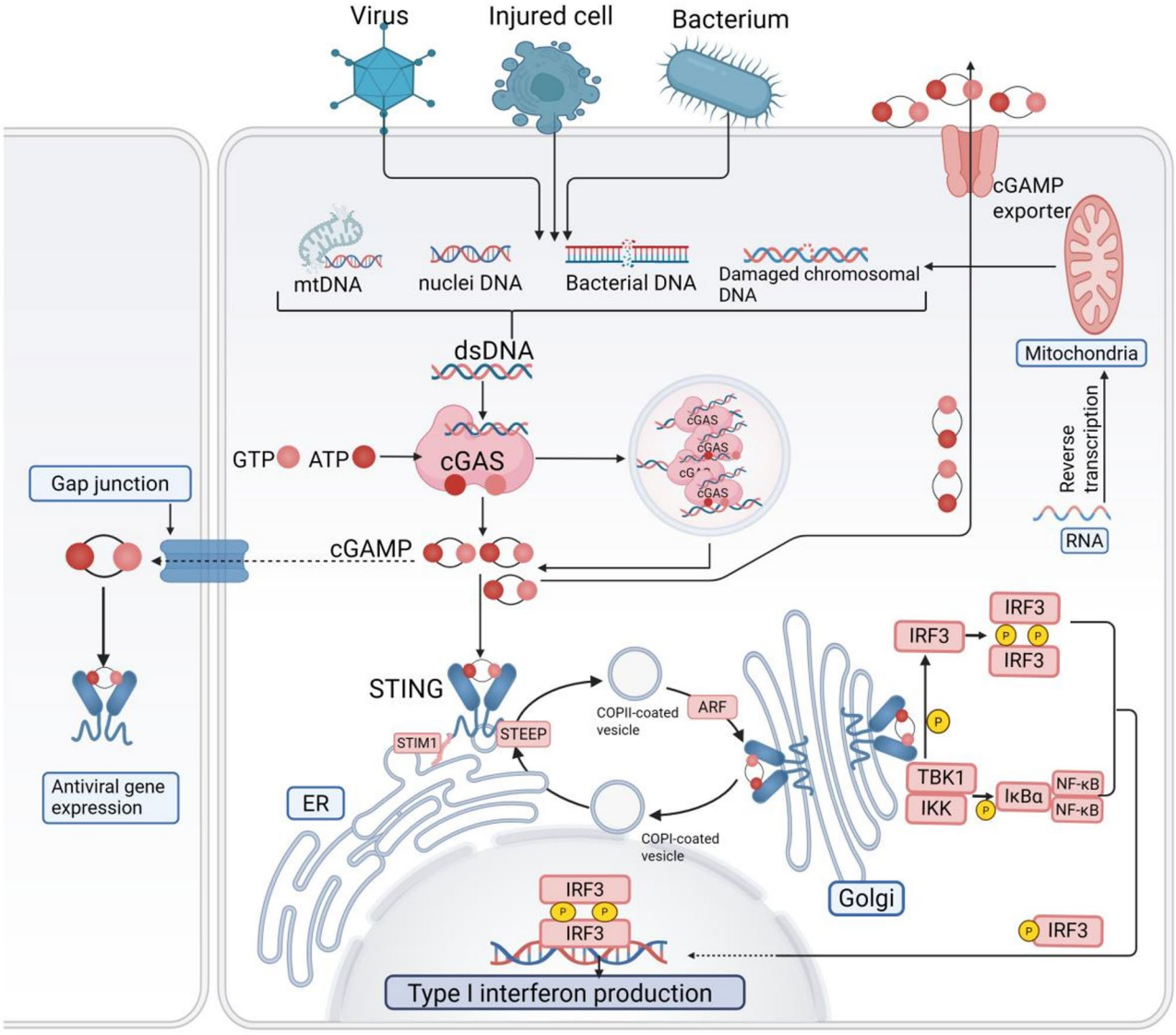

Fig. 1 Schematic diagram of the cGAS-STING signaling pathway mechanism. The cGAS-STING pathway serves as the central regulatory network for cytoplasmic DNA-triggered immune responses. The cytosolic DNA sensor cGAS recognizes aberrant dsDNA, such as nuclear or mitochondrial DNA leakage caused by DNA viral infection, genomic instability, or radiotherapy-/chemotherapy-induced damage. This recognition induces conformational changes and activates cGAS. Activated cGAS synthesizes the second messenger molecule cGAMP from ATP and GTP. cGAMP binds to STING on the ER, triggering its conformational rearrangement and subsequent translocation from the ER to the Golgi apparatus. Following palmitoylation at the Golgi, STING recruits TBK1. TBK1 phosphorylates the C-terminal domain of STING and facilitates the recruitment of IRF3. Phosphorylated IRF3 dimerizes, translocates to the nucleus, and initiates the transcription of IFN-I, thereby activating downstream immune responses. Concurrently, the STING-TBK1 signaling axis activates IRF3 and NF-κB, respectively, to induce the expression of IFN-I and pro-inflammatory factors. Subsequently, IFN-I synergistically enhances immune responses through downstream signaling pathways. This cascade enhances immune processes such as antigen presentation, T cell activation, NK cell cytotoxicity, and antibody production. By bridging innate immunity and adaptive immunity, the cGAS-STING pathway reshapes the TIME into an immunostimulatory niche, offering a promising therapeutic target for cancer immunotherapy

constitutes its catalytic core, comprising three functional modules: a dsDNA recognition domain, a catalytic core, and zinc-binding motifs [16]. Under the bridging action of zinc ions, dsDNA binds two cGAS molecules to drive complex assembly into a 2:2 cGAS-dsDNA stoichiometric configuration, thereby activating the cGAS enzyme [17]. The dimerized cGAS adopts a head-to-head orientation along DNA, assembling into a stable ladder-like network architecture either along a long, curved dsDNA helix or between two distinct dsDNA fragments [18, 19]. This unique interaction mode synergistically enhances the stability of individual cGAS-dsDNA complexes [20]. Notably, cGAS activation involves not only its C-terminal catalytic domain but also precise regulation by the N-terminal disordered domain through phase separation. Enriched with positively charged residues, this domain

cooperates with zinc ions and long dsDNA to induce liquid-liquid phase separation (LLPS), forming dynamic condensates [21]. This phase transition exhibits strict concentration dependence, initiating only when dsDNA exceeds a critical threshold, thereby ensuring precise spatiotemporal control of cGAS signaling activation [19, 22].

cGAS mediated signal cascade

Upon cooperative interaction between cGAS and dsDNA, structural rearrangements reposition the catalytic pocket to facilitate ATP and GTP substrate binding, thereby catalyzing the synthesis of the critical second messenger molecule-cGAMP [23]. Subsequently, cGAMP diffuses intracellularly and binds to the STING protein anchored on the endoplasmic reticulum (ER) membrane, inducing its conformational changes and triggering downstream immune responses [24]. In the resting state, STING remains tethered to the ER membrane via its interaction with the Ca^{2+} sensor stromal interaction molecule 1 (STIM1), where its cytoplasmic domain forms a V-shaped ligand-binding pocket oriented toward the cytosol to accommodate cGAMP [25]. Under activation conditions (when cGAS cooperates with dsDNA), cGAMP binding induces tight closure of STING's ligand-binding pocket, prompting a 180-degree rotation of the ligand-binding domain relative to the transmembrane domain. This conformational shift drives further polymerization of STING's C-terminal domain [26, 27]. Following this, STING undergoes higher-order oligomerization to form tetramers and translocates from the ER to the Golgi apparatus via the coat protein complex II (COPII) and ADP-ribosylation factor (ARF) GTPase-mediated transport machinery [28, 29]. Upon reaching the Golgi, STING undergoes palmitoylation at two cysteine residues (Cys88 and Cys91), a post-translational modification essential for its activation [30]. Palmitoylated STING recruits TANK-binding kinase 1 (TBK1), which phosphorylates the C-terminal domain of STING and facilitates the recruitment of interferon regulatory factor 3 (IRF3). The dimerized IRF3 then translocates to the nucleus to initiate transcription of IFN-I and interferon-stimulated genes (ISGs) [31]. Concurrently, the STING-TBK1 signaling axis activates the IκB kinase (IKK) complex, leading to phosphorylation of the NF-κB inhibitor IκBα. This triggers polyubiquitination and proteasomal degradation of IκBα, thereby releasing NF-κB for nuclear translocation and activation of downstream gene transcription [32]. Upon signal termination, STING is trafficked to endolysosomes for degradation [33].

The cGAS-STING pathway in cancer: a molecular switch for immune activation

It has long been recognized that DNA can trigger immune responses, even before DNA was established as the carrier of genetic information [34]. Under normal physiological conditions, DNA is strictly unaffiliated with the cytoplasm in eukaryotic cells to avoid autoimmunity [35]. However, in tumor cells, endogenous factors (such as genomic instability, chromosome segregation errors, and oxidative stress) and exogenous stimuli (such as chemotherapy and radiotherapy) can lead to leakage of nuclear DNA and mtDNA into the cytoplasm, thereby activating the cGAS-STING pathway [36]. Upon activation, STING forms oligomers that drive diverse downstream effects, most notably the initiation of the IRF3- and NF-κB-dependent signaling cascades [37]. Activated IRF3 dimerizes and translocates to the nucleus to initiate transcription of IFN-I, tumor necrosis factor (TNF), and interleukin-6 (IL-6). The production of IFN-I plays a crucial role in anti-tumor immunity, including promoting the priming of T cells against tumor-associated antigens (TAA), enhancing the accumulation of dendritic cells (DCs) within tumors, and activating the cross-presentation of tumor-antigen-specific T cells [38]. Through these mechanisms, the cGAS-STING pathway can link innate immunity and adaptive immunity, triggering a stronger anti-tumor immune response [39].

Dynamic regulatory network of the cGAS-STING pathway in TIME

The TIME, composed of tumor cells, endothelial cells, diverse immune cells, and complex extracellular matrix components, serves as a critical site for tumor-immune system interactions [40]. Within the TIME, the cGAS-STING signaling pathway mediates intercellular communication and engages in crosstalk with various components of the microenvironment, forming an intricate regulatory network involved in immune modulation, cellular development, and sustained tumor progression. Therefore, targeting the cGAS-STING pathway in immune compartments is crucial for remodeling the tumor-suppressive immune microenvironment. The specific mechanisms are discussed below [41, 42].

Immune cells

cGAS-STING pathway and DCs

DCs are highly specialized tissue-surveilling cells in the natural antitumor immune paradigm, equipped with a array of receptors to detect DAMPs or PAMPs [43–45]. Although the immune system's task of filtering and responding to oncogenic signals emitted by tumor tissue is exceedingly complex, the broad expression of innate receptors in DCs enables them to effectively recognize diverse tumor growth-associated byproducts, such as tumor-derived DNA present in the TIME [43]. Tumor DNA uptake by intratumoral DCs triggers the activation of the cytoplasmic DNA-sensing cGAS-STING pathway, which is essential for IFN-I induction [46]. IFN-I

upregulation further amplifies the pleiotropic effects of the cGAS-STING pathway on immune cells, thereby bolstering adaptive immunity mediated by effector T cells [47, 48]. Current research on the cGAS-STING signaling pathway has revealed a strong correlation between IFN-I production and its activation in DCs. Studies demonstrate that STING activation via the cGAS-STING pathway significantly enhances the activity of plasmacytoid dendritic cells (pDCs) and conventional dendritic cells (cDCs) in both murine models and human tumor microenvironments, while markedly elevating IFN-I secretion levels [49]. Notably, these studies also highlight cross-species differences in cell death responses triggered by STING activation, particularly the rapid depletion of pDCs observed in murine models, underscoring the importance of investigating STING signaling's subtype-specific regulatory mechanisms across DC subsets. Given the unique antigen-capturing and innate immune-sensing mechanisms of distinct DC subtypes, as well as their differential capacities for internalized antigen processing, cytokine production, and T cell activation, elucidating the functional states of the cGAS-STING pathway within specific DC subsets in the TIME holds critical implications for antitumor immunity (Fig. 2).

cDC$_1$

Conventional type 1 dendritic cells (cDC$_1$) perform the antigen-cross-presentation process necessary to initiate CD8$^+$ T cells activation [50]. This process relies on the high efficiency of Major Histocompatibility Complex Class I (MHC-I) to present tumor antigens, which is the core link of cDC$_1$ activation of specific immune response [51, 52]. Studies in mice with deficiencies in specific antigen-presenting cell subsets revealed that the nanoparticle

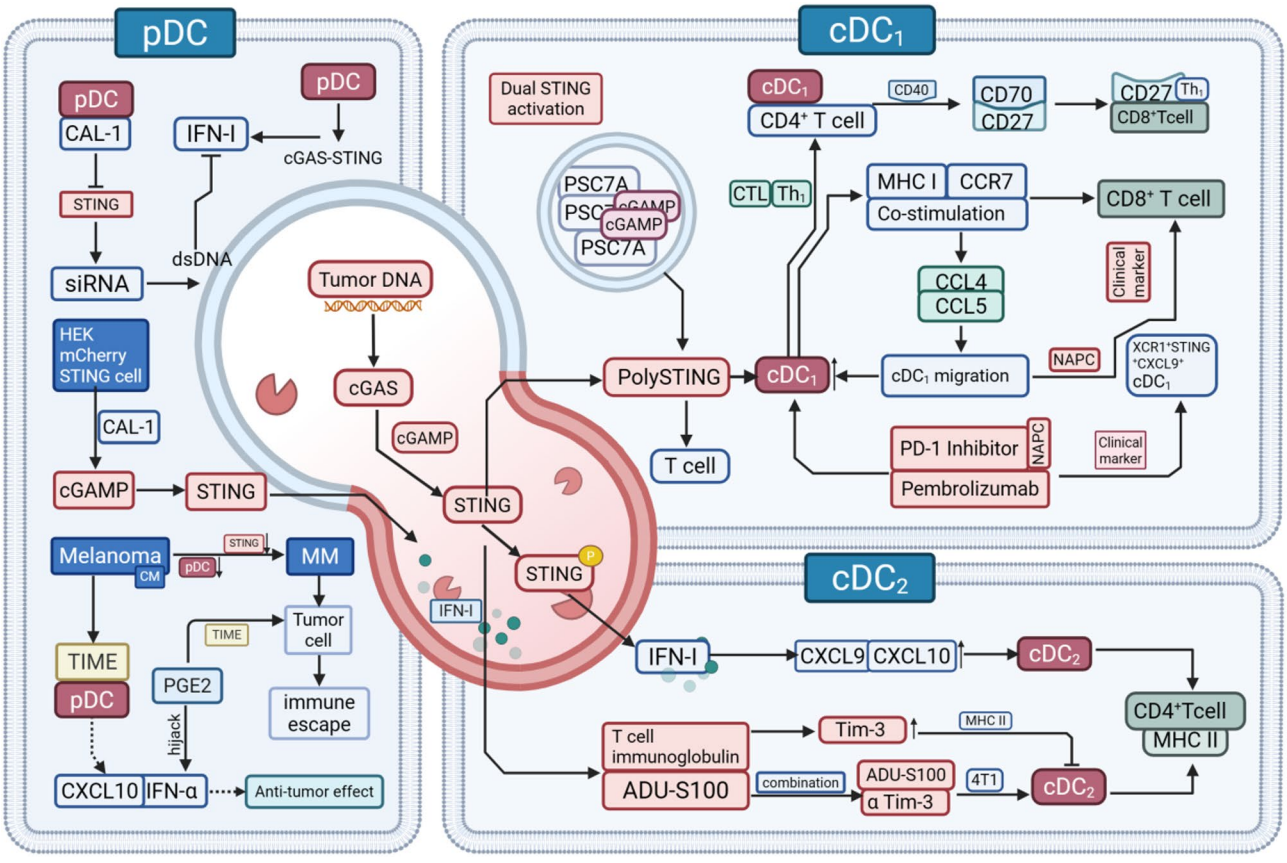

Fig. 2 Mechanisms and Roles of cGAS-STING Pathway in Regulating DC Subpopulations for Antitumor Immunity. This figure illustrates the activation mechanisms of the cGAS-STING signaling pathway in different DC subpopulations (pDCs, cDC$_1$, and cDC$_2$) and its impact on tumor immunity. After tumor-derived DNA enters the cytoplasm of DCs, it activates the cGAS-STING pathway, inducing the production of IFN-I, which in turn promotes the maturation of DC subpopulations and T cell activation. Specifically, pDCs sense tumor-derived DNA through the intracellular cGAS-STING pathway, inducing the production of IFN-I and subsequently activating downstream immune responses. However, in the TIME, the STING signaling pathway in pDCs may be inhibited, leading to immune evasion. cDC$_1$ is a key cell type for initiating CD8$^+$ T cell activation. The nanoparticle STING agonist PolySTING can specifically activate the STING-IFN-I signaling axis in cDC$_1$, enhancing its ability to cross-present antigens and driving CD8$^+$ T cell-mediated antitumor immune responses. Additionally, IFN-I secreted by a subset of activated CD4$^+$ T cells can enhance the activation capacity of cDC$_1$ towards CD8$^+$ T cells. cDC$_2$ plays a central role in initiating the naïve CD4$^+$ T cell immune response. The combination of the STING agonist ADU-S100 with anti-TIM-3 immune checkpoint blockade therapy can promote cDC$_2$ maturation and functional optimization, leading to enhanced CD4$^+$ T cell activation and tumor infiltration

STING agonist PolySTING, through targeted delivery, activates the STING-IFN-I signaling axis in cDC_1, significantly enhancing their infiltration into the TIME and amplifying the cross-presentation capacity, thereby driving $CD8^+$ T cell-mediated antitumor immunity [53]. This effect manifests as robust tumor growth suppression in preclinical non-small cell lung cancer (NSCLC) models, with therapeutic efficacy positively correlating with prolonged patient survival. Based on these findings, researchers propose that STING pathway activation signatures in cDC_1 could serve as novel prognostic biomarkers to predict responses to cancer immunotherapy, providing a theoretical foundation for personalized treatment strategies. Notably, cGAS-STING pathway activation in cDC_1 exhibits multi-layered regulatory features. Recent studies demonstrate that virus-like particle-encapsulated cGAMP also requires STING activation within cDC_1 to exert antitumor effects, underscoring the pathway's central role across diverse drug delivery approaches [54]. Transcriptomic analyses further reveal that specific $CD4^+$ T cell subsets in the TIME secrete IFN-I to provide "licensing signals" to cDC_1, augmenting their ability to activate $CD8^+$ T cells—a cellular crosstalk strongly associated with improved overall survival in cancer patients [55–57]. Collectively, these insights highlight that precise modulation of this pathway, particularly through cDC_1-specific targeted delivery systems, holds promise for overcoming current immunotherapy limitations and advancing personalized cancer immunotherapies.

cDC_2

Conventional type 2 dendritic cells (cDC_2), as the key antigen-presenting cells initiating the $CD4^+$ T cell immune response, play a central regulatory role in the adaptive immune response [58]. In response to the clinical challenge of STING monotherapy resistance in the TIME, Luo and colleagues systematically evaluated the synergistic anti-tumor effect of the STING agonist ADU-S100 and anti-TIM-3 immune checkpoint blockade therapy by constructing a 4T1 mouse tumor model. Mechanistic studies showed that blocking TIM-3 promotes the maturation and differentiation of cDC_2 by upregulating the expression of major histocompatibility complex class II (MHC-II) and co-stimulatory molecules CD80/CD86. This enhanced the activation and tumor infiltration of $CD4^+$ T cells, reduced tumor load, and prolonged the survival of tumor-bearing mice [59]. These findings suggest that immune regulation strategies based on cDC_2, especially therapies targeting the STING pathway, may provide a new approach to improving tumor immunotherapy efficacy.

pDCs

Plasmacytoid dendritic cells (pDCs) are less capable of priming naïve T cells than conventional DC subtypes, but they are potent producers of IFN-I and key players in antiviral and antitumor immunity [60]. One of the key mechanisms of pDCs activation involves the cGAS-STING signaling pathway, an intracellular DNA-sensing pathway. Bode and colleagues used the human pDC cell line CAL-1 to perform siRNA (small interfering RNA, which specifically silences target genes) experiments and found that knocking down STING significantly reduced IFN-I secretion in response to double-stranded DNA stimulation. To clarify STING's function, the researchers constructed a genetically engineered reporter system: STING protein tagged with an mCherry fluorescent label was expressed in human embryonic kidney cells, and cGAMP—the second messenger produced by CAL-1 under DNA stimulation—was confirmed via fluorescent tracing to activate the STING pathway across cells and drive IFN-I production. These results demonstrate the critical role of the cGAS-STING pathway in pDCs' ability to sense intracellular DNA and initiate IFN-I responses [61]. However, in the TIME, the cGAS-STING signaling pathway is often inhibited, leading to pDCs dysfunction. In primary cutaneous melanoma, STING signaling intensity in pDCs was observed to decrease gradually with disease progression and collapse almost completely in metastatic melanoma [62]. This suggests that tumor cells may actively reshape TIME to evade immune surveillance. This inhibition likely involves multiple mechanisms, such as tumor cell secretion of inhibitory cytokines, recruitment of immunosuppressive cells, or direct post-translational modification of STING protein [63]. Taken together, these studies reveal that the cGAS-STING signaling pathway is a key driver of pDC activation, IFN-I is a core mediator of pDC-mediated antitumor effects, and TIME disrupts this immune defense mechanism. Therefore, a comprehensive understanding of pDCs activation mechanisms—particularly the role of cGAS-STING signaling—and how TIME subverts these pathways is critical for developing more effective cancer immunotherapy strategies [64].

cGAS-STING pathway and T cells

T cells are central mediators of tumor immune surveillance, capable of identifying and eliminating transformed cells through antigen-specific recognition [65]. However, tumors establish an immunosuppressive microenvironment, that suppresses T cell function, enabling tumor persistence and progression. Over the past decade, studies have elucidated the multifaceted roles of the cGAS-STING signaling pathway across T cell subpopulations, as summarized below (Fig. 3).

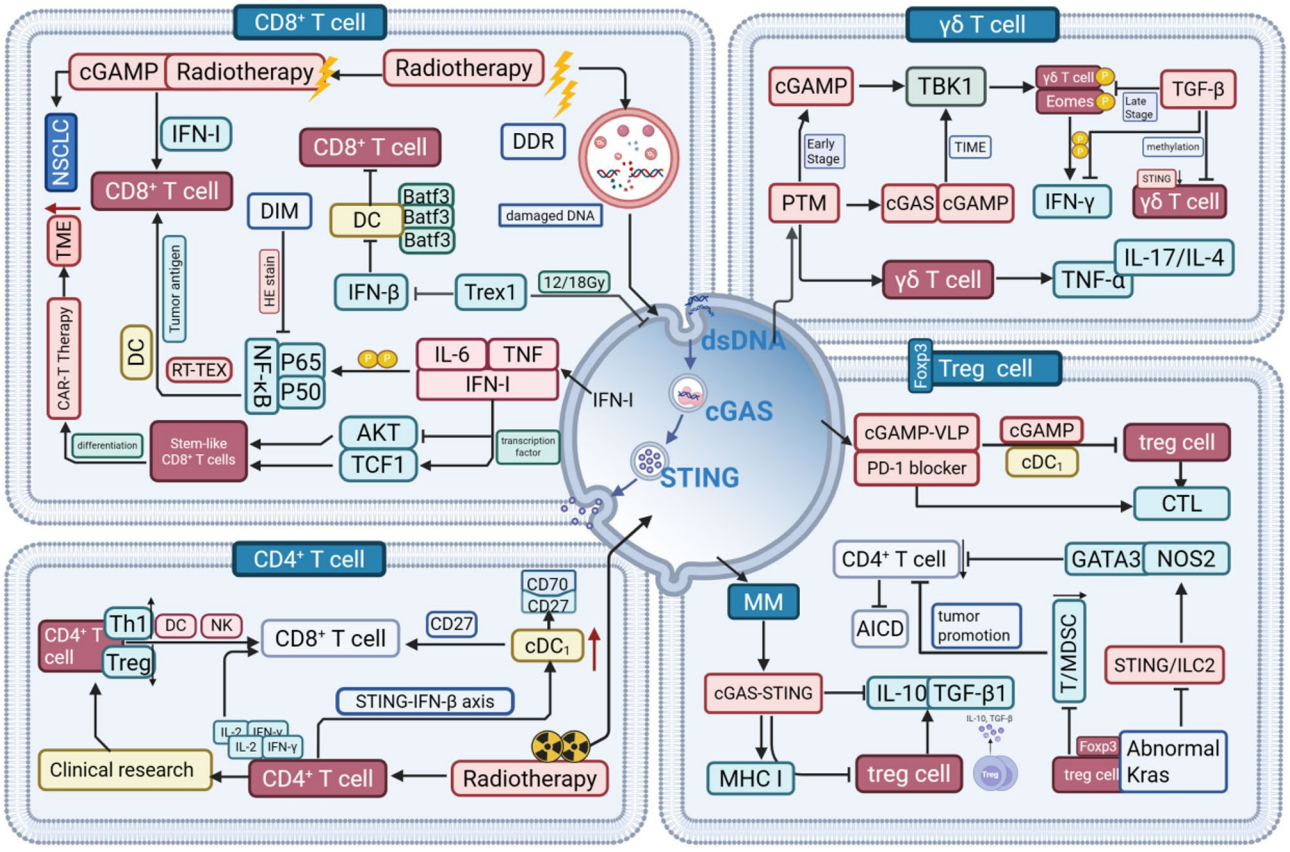

Fig. 3 Mechanism and effects of the cGAS-STING pathway in regulating antitumor immunity across T cell subsets. In $CD8^+$ T cells, cGAS-STING activation enhances tumor infiltration by inducing IFN-I secretion and sustains stem-like properties through transcriptional factor TCF1 upregulation, thereby promoting the durable antitumor activity of CAR-T cells. Concurrently, IFN-I signaling inhibits the Akt pathway to drive their differentiation into cytotoxic effector cells. $CD4^+$ T cells, as pivotal early responders, establish a pro-inflammatory microenvironment via IL-2 and IFN-γ secretion. Through the STING-IFN-β axis, they engage in bidirectional crosstalk with cDC_1, enhancing antigen presentation and priming $CD8^+$ T cell activation.The cGAS-STING pathway also precisely regulates γδ T cells: In early tumors, cGAMP promotes the production of IFN-γ through the phosphorylation of Eomes, while in the immune microenvironment of advanced tumors, TGF-β inhibits the expression of STING protein in γδ T cells through epigenetic mechanisms, leading to functional exhaustion of γδ T cells. In treg cells, cGAS-STING activation disrupts immunosuppressive functions by downregulating IL-10 and TGF-β1 production, upregulating tumor MHC-I expression, and reversing immune tolerance. Moreover, STING-based vaccines further amplify T cell-mediated immunity by suppressing treg differentiation

$CD8^+$ T cells

Functional, tumor-specific $CD8^+$ cytotoxic T lymphocytes drive the adaptive immune response to cancer. Thus, induction of their activity is the ultimate aim of all immunotherapies [66]. In recent years, the cGAS-STING pathway, as a potential target for immunotherapy of solid tumors, has been verified to revive antitumor immunity mediated by $CD8^+$ T cells [67]. In lung cancer radiation therapy (RT), activation of the cGAS-STING pathway has been found to significantly increase the infiltration of $CD8^+$ T cells by promoting the secretion of IFN-I, effectively stimulating the anti-tumor immune response in vivo and showing great anti-tumor potential [68]. Besides, it has also been observed that the cGAS-STING signaling capability in peripheral blood $CD8^+$ T cells from cancer patients is markedly diminished, which directly impairs the sustained anti-tumor activity of adoptive transfer T cells, such as CAR T cells. Mechanistically, on the one hand, activation of the cGAS-STING pathway can induce the expression of transcription factor TCF1, maintain the stem-like characteristics of $CD8^+$ T cells, and ensure the continuous expansion of the immune memory pool. On the other hand, autocrine IFN-I signaling can inhibit the Akt signaling pathway, driving the differentiation of naïve $CD8^+$ T cells into more mature and cytotoxic effector cells, and ultimately enhancing the anti-tumor effect of CAR-T cell therapy [69]. In conclusion, by enhancing cGAS-STING signal transduction, the expression of IFN-I-related genes and the strong immune activation of $CD8^+$ T cells are induced, which is expected to transform the immunosuppressive microenvironment into an immune-activated state, thereby enhancing the effect of cancer immunotherapy.

CD4⁺ T cells

CD4⁺ T cells also make an important contribution to antitumor immunity. Studies have shown that cGAS-STING signal transduction plays an indispensable role in CD4⁺ T cell development and effector function [70, 71]. Previous studies indicated that RT can enhance the infiltration of CD8⁺ T cells and antigen recognition through STING activation. However, dynamic immune monitoring by Martin's team revealed that RT-induced tumor microenvironment remodeling exhibits temporal characteristics: the early infiltration of B cells and CD4⁺ T cells precedes that of CD8⁺ T cells, and this spatiotemporal dynamic feature reshapes the topology of the TIME. B cells activate CD4⁺ T cells through cross-presentation of neoantigens, and these activated CD4⁺ T cells secrete IL-2 and IFN-γ to establish a pro-inflammatory niche, laying the molecular foundation for the subsequent deep infiltration and clonal expansion of CD8⁺ T cells, thereby achieving synergistic control of primary and metastatic lesions [72]. This finding is suggestive and implies that greater attention should be paid to the role of early-infiltrating CD4⁺ T cells. Further studies found that activated CD4⁺ T cells establish a bidirectional dialogue with cDC_1 through the STING-IFN-β axis. CD4⁺ T cell-derived IFN-β not only enhances the expression of MHC-I molecules on cDC_1 to maintain positive feedback of self-activation but also enables cDC_1 to acquire efficient cross-presentation ability by upregulating co-stimulatory molecules such as CD80 and CD86, thereby transforming tumor antigens into functional signals for CD8⁺ T cells and completing the cascade amplification effect from innate to adaptive immunity [55]. In translational clinical studies, He and colleagues demonstrated the critical role of CD4⁺ T cells in enhancing the efficacy of in situ vaccines. As the first responders, CD4⁺ T cells induce strong polarization of type 1 helper T cells (Th1) in in-situ vaccines based on the STING protein. Th1 polarization suppresses the differentiation of regulatory T (treg) cells breaking the situation of tumor immunosuppression [73].

Treg cells

Treg cells expressing the transcription factor Foxp3 exert a highly immunosuppressive effect. In malignant tumors, treg cells contribute to the formation of an immunosuppressive microenvironment and promote immune tolerance [74]. Earlier studies have demonstrated that cGAS-STING signal transduction plays a crucial role in the treg-driven immune cascade and tumor metastasis. Although the specific mechanisms may vary by tumor type, a common observation is that the activation of cGAS-STING signaling is closely associated with a reduction in the immunosuppressive effects mediated by treg cells. For instance, in the immunosuppressive microenvironment of multiple myeloma (MM), activation of the cGAS-STING pathway can inhibit the accumulation of treg cells, decrease the production of immunosuppressive cytokines such as IL−10 and TGF-β1, and enhance the expression of MHC Class I molecules on tumor cells [75]. This suggests that cGAS-STING pathway activation may weaken the immunosuppressive capacity of treg cells by reshaping the TIME, thereby promoting tumor antigen presentation and T cell activation. Similarly, in a chemotherapy-resistant model of Kras-mutated lung cancer, treg cells were found to enhance GATA3/NOS2-associated immunosuppression by inhibiting the STING/ILC2 axis, ultimately leading to reduced CD4⁺ T cell infiltration and an increased risk of lung metastasis [76]. This indicates that tumor cells may exploit treg cells to inhibit STING signaling, thereby evading immune surveillance and facilitating tumor metastasis. Consequently, targeting the cGAS-STING pathway to deplete immunosuppressive treg cells holds promise for overcoming a critical bottleneck in immune-mediated cancer control [77].

γδ T cells

γδ T cells play a critical role in tumor immunity by providing an early source of Interferon-γ (IFN-γ) [78]. Their effector functions are tightly regulated by the cGAS-STING signaling pathway [79]. Emerging evidence highlights that post-translational modifications (PTMs) mediated by cGAS-STING pathway orchestrate the dual roles of γδ T cells during tumor progression. In early-stage tumors, tumor-derived cGAMP activates the TBK1-Eomes axis, driving IFN-γ production and enhancing anti-tumor surveillance. Conversely, in advanced tumor microenvironments, Transforming Growth Factor-beta (TGF-β) epigenetically silences STING expression in γδ T cells via promoter methylation, resulting in functional exhaustion and impaired immune surveillance [80]. Notably, the study by Serrano's team further revealed the transformation potential of STING ligands in γδ T cells immunotherapy. In vitro experiments confirmed that STING signaling can intricately regulate the activation threshold of human γδ T cells and the efficiency of tumor cell cleavage, providing key conditions for optimizing in vivo γδ T cell immunotherapy [81]. Notably, STING ligands exhibit transformative potential in γδ T cell immunotherapy. Preclinical studies demonstrate that STING activation dynamically regulates the activation threshold of human γδ T cells and their tumor-lytic efficiency, providing a rationale for optimizing adoptive cell therapy protocols. Furthermore, PTMs not only directly modulate γδ T cell effector functions but also maintain immune homeostasis by coordinating cytokine networks in innate immune cells [82]. These multi-layered regulatory mechanisms underscore the therapeutic potential of targeting the cGAS-STING pathway to develop combination immunotherapies.

cGAS-STING pathway and Tumor-associated macrophages

Macrophages, known as the "scavengers" of the body, are capable of phagocytosing pathogens and presenting antigens through the formation of MHC complexes by processing antigens [83, 84]. Upon migrating into the TIME, they differentiate into tumor-associated macrophages (TAMs), which play a pivotal role in initiating and modulating anti-tumor immune responses [85]. Based on distinct activation pathways, functional profiles, and cytokines secreted post-polarization, TAMs are broadly categorized into two subsets: classically activated M_1 TAMs (generally recognized as anti-tumor) and alternatively activated M_2 TAMs (typically pro-tumorigenic) [86]. Recent studies have demonstrated that cGAS-STING signaling critically regulates macrophage phenotypic plasticity, thereby exerting a significant impact on TIME remodeling. This review provides a concise overview of the cGAS-STING pathway and its crosstalk with TAMs, aiming to advance novel theoretical frameworks and potential therapeutic strategies for tumor immunotherapy (Fig. 4).

M_1 TAMs

M_1 TAMs are induced by molecules such as IFN-γ, lipopolysaccharide (LPS), or granulocyte-macrophage colony-stimulating factor (GM-CSF), and they play a classical role in promoting inflammation and killing tumor cells through the release of inflammatory cytokines like IL−1 [87]. In recent years, several studies have explored the specific mechanisms by which the activation of the cGAS-STING pathway promotes M_1 TAM polarization. For instance, in the context of immunotherapy for hepatocellular carcinoma (HCC), it has been found that activating the cGAS-STING pathway can drive tumor-associated macrophages toward M_1 polarization, enhancing T lymphocyte infiltration and inhibiting the progression of HCC [88]. Additionally, this pathway can induce PD-L1 expression through the

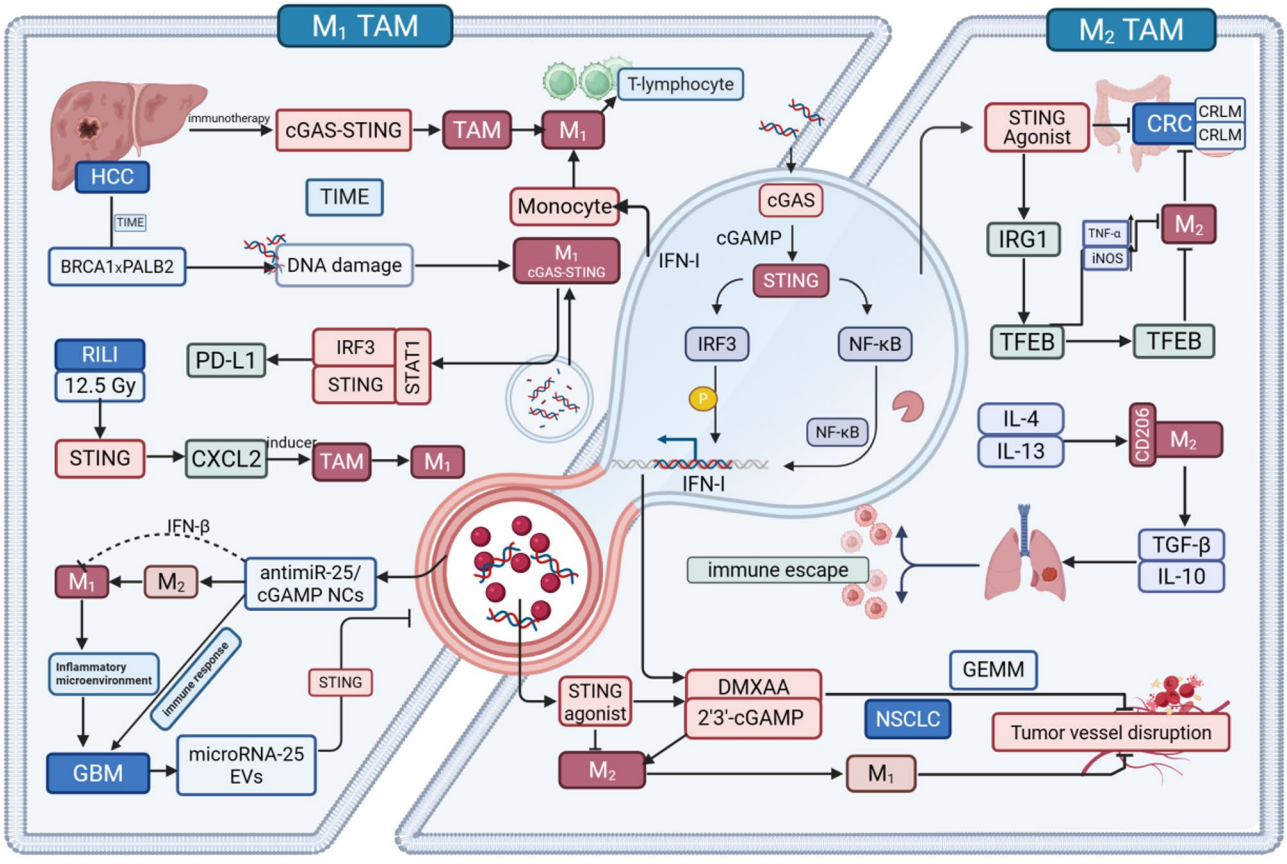

Fig. 4 The cGAS-STING pathway regulates TAM polarization and anti-tumor immune effect. Within the TIME, M_1 TAMs, induced by IFN-γ or LPS, exhibit pro-inflammatory and tumoricidal properties. cGAS-STING activation drives M_1 polarization via the STING-IRF3-STAT1 axis, promoting T cell infiltration and enhancing anti-tumor immunity, albeit with a potential trade-off of inducing PD-L1 expression to foster immune suppression. For instance, in hepatocellular carcinoma, cGAS-STING activation enhances anti-PD-1 therapy efficacy, while in models of radiation-induced lung injury, STING-mediated upregulation of CCL2 recruits M_1 TAMs. In contrast, M_2 TAMs induced by IL-4/IL-13, secrete IL-10 and TGF-β, express high levels of CD206, and promote immune evasion. Moreover, STING agonists or nanoparticle-based drug delivery systems can reverse M_2 polarization, reprogramming these cells into an M_1-like phenotype to amplify anti-tumor effects. In glioblastoma and colorectal cancer liver metastasis models, STING activation suppresses M_2 functionality and reduces metastatic potential through IFN-I secretion or the IRG1-TFEB axis, respectively

STING-IRF3-STAT1 axis, leading to tumor immunosuppressive niche. This dual effect of immune suppression and T cell infiltration results in a better response of HCC to anti-PD−1 therapy and provides new targets and strategies for reshaping the TIME [88]. Furthermore, in a study aimed at alleviating radiation-induced lung injury (RILI) in lung cancer patients, it was observed that significantly activated STING signaling stimulated an increase in the cytokine CCL2. CCL2 acts as a chemotactic agent, promoting the polarization of macrophages toward an M1-like phenotype, thereby initiating an effective immune response [89]. Given the critical roles of TAMs and the cGAS-STING pathway in immune responses and tissue damage, elucidating the complex relationships and molecular mechanisms between STING signaling, macrophages, and the development of RILI will enhance our understanding of the immune response to radiation-induced damage. This knowledge may also influence the development of therapeutic strategies targeting the cGAS-STING pathway in the context of RILI [90].

M_2 TAMs

The infiltration of TAMs characterized by the M_2 phenotype is an important feature of malignant tumors [91]. M_2*TAMs* can be induced by IL−4 and IL−13, primarily characterized by the overexpression of CD206 (which enhances phagocytic capacity) and the secretion of anti-inflammatory cytokines such as IL−10 and TGF-β, thereby playing corresponding roles in tissue repair, wound healing, and tumor progression [92, 93]. Studies have shown that activating the cGAS-STING pathway can alter the phenotype of M_2*TAMs*, promoting their conversion to an anti-tumor phenotype, thereby reducing tumor burden [94]. For example, in a mouse model of NSCLC, researchers successfully repolarized bone marrow-derived M_2 macrophages to M_1 macrophages using the STING agonist DMXAA and 2'3'-cGAMP, inducing tumor site-specific vascular destruction and alleviating tumor burden in the mouse model [95]. A similar phenomenon has been observed in the immune microenvironment of glioblastoma (GBM), where a large number of infiltrating M_2 TAMs promote tumor immune evasion by secreting immunosuppressive factors [96]. To address this mechanism, Petrovic and colleagues utilized an antimiR−25/cGAMP nanocomplex to activate the cGAS-STING pathway in TAMs, upregulating IFN-I expression, which not only drives the conversion of M_2 TAMs to M_1 TAMs but also synergistically enhances systemic anti-tumor immune responses [96]. More importantly, STING activation can also reduce tumor invasion and metastatic potential by inhibiting M_2 TAM polarization. In colorectal cancer liver metastasis, STING promotes the nuclear translocation of transcription factor EB (TFEB) by activating immune response gene 1 (IRG1), inhibiting M_2 TAMs in the microenvironment and reducing the invasive capacity of metastatic foci [97]. Furthermore, intervention strategies targeting macrophage plasticity are gradually becoming more innovative. Li and colleagues developed a polymer nanoplatform that can activate the cGAMP-mediated STING pathway within TAMs, significantly reducing the expression of signal regulatory protein alpha (SIRPα) and facilitating the transition of M_2 TAMs to M_1 TAMs. This approach enhances the phagocytic effects of cancer immunotherapy in a melanoma transplantation model and significantly alleviates the burden of lung metastasis [98]. In summary, the above studies provide original insights into the potential role of the STING pathway in macrophage-based immunotherapy and offer potential combinatorial strategies for cancer treatment.

cGAS-STING pathway and Natural Killer cells

Unlike antigen-specific T cells, Natural Killer (NK) cells can directly recognize and eliminate target cells without prior antigen exposure or MHC restriction [99]. This unique capability underscores their pivotal role in immune responses and positions them as critical targets in cancer immunotherapy [100]. Recent advances have expanded our understanding of the immunomodulatory potential of the cGAS-STING pathway, revealing its multifaceted regulation of NK cell recruitment, activation, and cytotoxic functions [101]. For instance, in hepatocellular carcinoma, genetic silencing or pharmacological inhibition of eukaryotic elongation factor 2 kinase (eEF2K) induces tumor cell DNA damage, activates the cGAS-STING pathway within malignant cells, and triggers robust secretion of chemokines such as IL−2 and CXCL9, thereby enhancing NK cell chemotaxis to tumor sites and augmenting their cytotoxic activity [102]. These findings demonstrate that tumor cell-autonomous STING activation indirectly modulates NK cell distribution and function through remodeling the chemokine microenvironment. To analyze the function of endogenous STING signals in NK cells, Chen and colleagues constructed an Ncr1iCre STINGf/f mouse model (NK cell-specific STING knockout), and found that its melanoma lung metastasis load was significantly higher than that of the control group. Moreover, Exogenous STING agonists (such as ADU-S100) can restore NK cells' IFN-γ secretion and tumor killing activity, and reverse $CD8^+$ T cells depletion phenotype [103]. This study confirmed that the intrinsic STING signaling in NK cells directly limits tumor progression through autonomous IFN-γ release and T cell cooperation. Recent research has also supported the importance of STING in NK cell function from an immunometabolic perspective. In NSCLC, the natural product Rocaglamide (RocA) induces mitochondrial autophagy inhibition, leading to mtDNA leakage

and triggering NK cell directional infiltration to tumor sites in a STING-dependent manner. This groundbreaking advancement reveals the molecular link between metabolic stress and spatial reprogramming of NK cells, providing new directions for optimizing immune cell infiltration strategies targeting the STING pathway [104]. In summary, the cGAS-STING pathway dynamically regulates NK cell recruitment, activation, and spatial localization through a tripartite regulatory network involving "tumor cells–immune microenvironment–intrinsic NK cell signaling". This multilayered interactive network is revolutionizing precision immunotherapy strategies centered on NK cells.

cGAS-STING pathway and myeloid derived suppressor cells

Myeloid derived suppressor cells (MDSCs) are a highly heterogeneous population of immature immune cells with immunosuppressive functions that are recruited to the TIME [105]. The ability of MDSCs to promote tumor growth by enhancing tumor survival, angiogenesis, metastasis, and pre-metastatic niche formation has been well-documented [106]. The majority of literature implies that STING signaling in the TIME could suppress MDSC recruitment, differentiation and function [106, 107]. For example, in studies using DNA virus-associated tumors, such as Nasopharyngeal Carcinoma (NPC), as a model, gain-of-function and loss-of-function experiments were employed to investigate the role of STING signaling in tumor cells and its impact on regulating tumor cell-MDSC crosstalk. These experiments demonstrated that STING signaling reduces the secretion of IL-6 and GM-CSF by inhibiting the STAT3 pathway, blocks the differentiation of NPC-derived MDSCs, and enhances antitumor immune responses [108]. Meanwhile, Pei and colleagues reported a combined study on the STAT3 signaling pathway and STING signaling, revealing that the STAT3 inhibitor HJC0152 synergizes with the STING agonist c-diAMP to reduce the infiltration of treg cells and MDSCs in tumors while increasing the accumulation of $CD8^+$ T cells in the TIME, thereby inducing an effective anti-tumor immune response [109]. Consistent with these findings, another study observed a significant increase in $CD11b^+Gr1^+$ immature MDSCs in $STING^{gt/gt}$ mice bearing gliomas, suggesting that STING signaling plays a protective role in tumor progression [110]. In vitro experiments further validated that the STING agonist cGAMP can inhibit the production of nitric oxide (NO) and reactive oxygen species (ROS) by MDSCs isolated from the spleens of B16 melanoma-bearing mice, thereby weakening the immunosuppressive function of MDSCs on T cells [111]. Moreover, as the ability of MDSCs to suppress T cell proliferation diminishes, their immunosuppressive characteristics are also lost. Although research on cGAS-STING signaling in MDSCs is limited, the importance of this signaling pathway cannot be overlooked. Elucidating the complex role of cGAS-STING in MDSCs presents an opportunity to develop new strategies for targeting TIME that may enhance sensitivity to cancer immunotherapy in the future.

cGAS-STING pathway and B cells

As central executors of humoral immunity, B cells exert multidimensional roles in tumor immunity through antigen presentation, antibody secretion, and cytokine modulation [112]. Recent studies have unveiled the intricate interplay between the cGAS-STING pathway and B cells within the tumor immunosuppressive microenvironment, particularly in promoting apoptosis. In a murine model of chronic lymphocytic leukemia, the STING agonist 3'3'-cGAMP not only suppressed tumor growth but also directly induced apoptosis of malignant B cells [113]. Concurrently, evidence demonstrates that B cells can be directly activated by bacterial CDNs in a STING-dependent manner both in vitro and in vivo, triggering caspase-dependent death programs while upregulating co-stimulatory molecules such as CD86 [114]. This dual mechanism promotes T cell cross-priming and establishes a "death-immunization" antitumor response [114]. However, clinical trials led by Li's team revealed that STING agonist monotherapy frequently induces adaptive resistance due to "signal overload". Mechanistic studies showed that aberrant STING activation drives pathological expansion of regulatory B cells (Bregs), which markedly suppress NK cell cytotoxic function via IL-35 secretion, thereby reinforcing the immunosuppressive tumor microenvironment [42]. This discovery molecularly elucidates a key limitation underlying the constrained clinical efficacy of STING agonists. Building on these insights, researchers have further deciphered the STING-Breg-NK cell interaction network and proposed an innovative combinatorial strategy in pancreatic cancer involving cGAMP and IL-35-neutralizing antibodies to synergistically block immunosuppressive signaling. This approach establishes a novel translational paradigm for overcoming therapeutic resistance in clinical settings (Fig. 5) [115].

Stromal cells

cGAS-STING pathway and cancer-associated fibroblasts

As pivotal components of the TIME, cancer-associated fibroblasts (CAFs) expressing STING protein exhibit functional heterogeneity finely regulated by the cGAS-STING pathway [116]. Studies demonstrate that this pathway bidirectionally modulates the differentiation of pro-tumoral (pCAFs) and anti-tumoral (rCAFs) subsets, directly driving malignant phenotypes such as immunosuppression, chemotherapy resistance, and stemness maintenance [117]. In pancreatic ductal adenocarcinoma

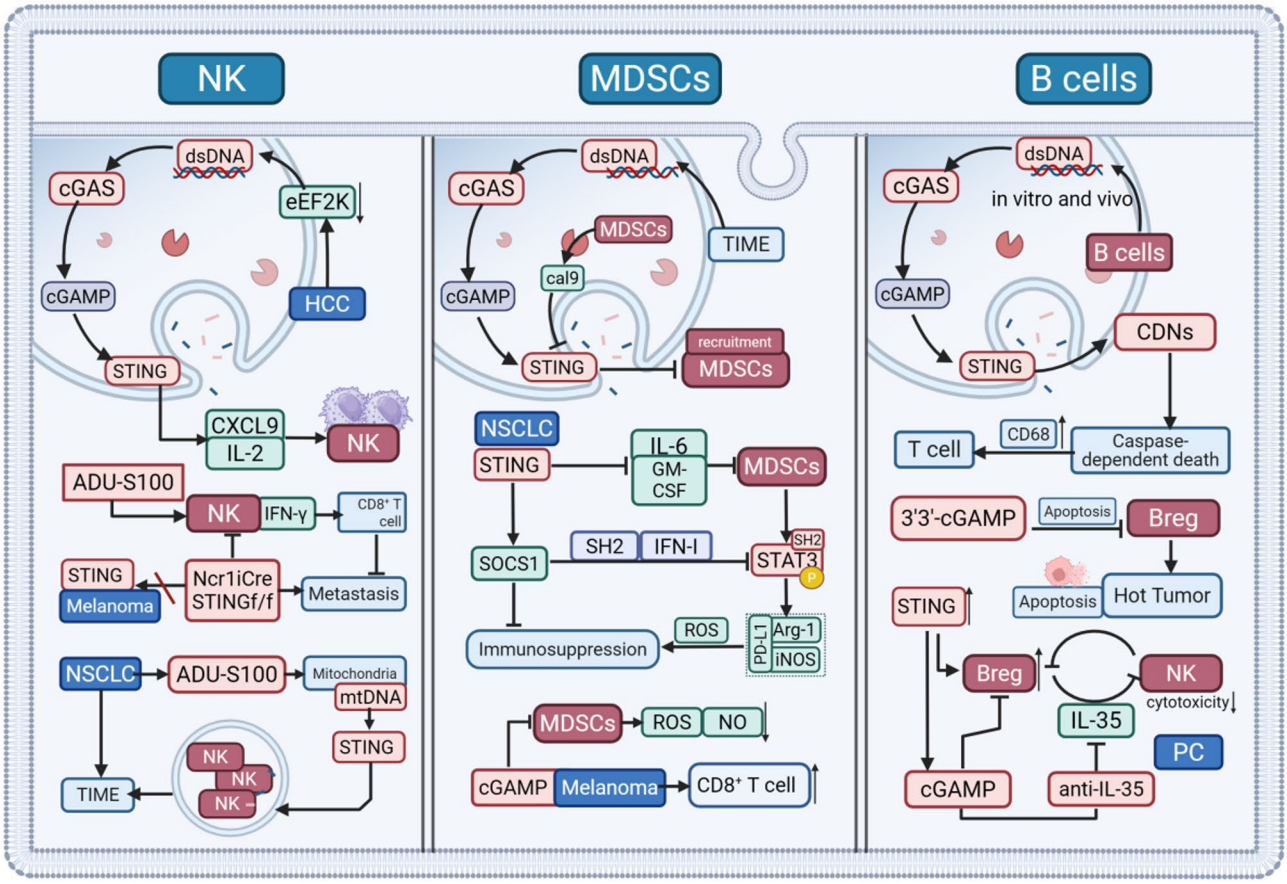

Fig. 5 The cGAS-STING interaction network with other immune cells and its regulatory role in tumor immunity. In NK cells, activation of the cGAS-STING pathway (such as via eEF2K inhibition-induced DNA damage) drives the secretion of chemokines such as IL-2 and CXCL9, enhancing NK cell recruitment to tumors and cytotoxic activity. Intrinsic STING signaling in NK cells further suppresses tumor metastasis through autonomous IFN-γ production and synergistic cooperation with $CD8^+$ T cells. For MDSCs, STING activation disrupts their differentiation and immunosuppressive functions by suppressing STAT3 signaling (such as via reduced IL-6/GM-CSF production). B cells exhibit dual regulation: The STING agonist cGAMP induces apoptosis of malignant B cells and activates T cell responses. However, excessive STING activation may trigger Breg amplification and inhibit NK cell cytotoxicity via IL-35

(PDAC), the dense stromal barrier formed by CAFs substantially compromises the efficacy of immune checkpoint blockade (ICB). However, in cGAS-STING double-positive PDAC cases, rCAFs marker expression is significantly elevated, accompanied by sustained cytotoxic $CD8^+$ T cell infiltration from stroma to tumor parenchyma. This mechanism is further validated in Transwell co-culture experiments: cGAS-STING activation reverses CAF-mediated blockade of immune cell infiltration and markedly enhances tumor cell killing efficiency [118]. These findings not only reveal novel mechanisms underlying PDAC immunotherapy resistance but also highlight cGAS-STING signaling as a potential target to potentiate ICB efficacy. In bladder cancer (BC), single-cell RNA sequencing reveals that tumor cell-intrinsic cGAS-STING activation induces differentiation of $SLC14A1^+$ CAFs via interferon signaling. This CAFs subset enhances tumor cell stemness and chemoresistance through WNT5A paracrine signaling. Clinical data correlate high $SLC14A1^+$ CAFs abundance with poor patient prognosis and diminished immunotherapy responsiveness, while STING inhibition impedes $SLC14A1^+$ CAFs formation, thereby sensitizing tumors to chemotherapy [119]. A parallel mechanism operates in ovarian cancer: cisplatin-induced tumor cell DNA damage can transfer to CAFs, activating the cGAS-STING-IFNβ1 axis in CAFs to promote IFN-β secretion and platinum resistance, an effect reversible by STING targeting [120]. Collectively, these studies underscore the cGAS-STING pathway as a central regulator of CAFs diversity and reveal critical links between tumor genomic instability and microenvironmental reprogramming. Future research should prioritize the development of CAFs subset-specific biomarkers and explore combinatorial strategies integrating cGAS-STING targeting with ICB or stromal remodeling approaches to achieve precise TIME modulation.

cGAS-STING pathway and mesenchymal stem cells

The role of mesenchymal stem cells (MSCs) in cancer progression has been extensively documented [121].

MSCs facilitate tumor metastasis by mediating bidirectional IFN-β transmission via the cGAS-cGAMP-STING signaling axis, thereby upregulating HLA-I expression in tumor cells to evade NK cell-mediated killing. Blockade of this signaling pathway restores NK cell sensitivity to tumor cells and suppresses metastasis, offering a novel therapeutic strategy for targeting tumor-MSC interactions [122]. Moreover, engineered MSCs can be repurposed as potent antitumor delivery vehicles. Studies have demonstrated that induced pluripotent stem cell-derived MSCs generate STING-activated extracellular vesicles (R-EVs), which trigger IFN-β expression in THP-1 monocytes via the cGAS-STING pathway and enhance antitumor immunity [123]. Further genetic engineering strategies have shown that MSCs can synergistically deliver a CDUPRT/5-fluorocytosine prodrug system along with IFN-β, achieving a 90% tumor suppression rate in a peritoneal carcinoma model [124].

Other factors

Beyond the direct involvement of immune and stromal cells in the TIME, soluble mediators-such as IL-6, IFN-I, and chemokines-play a pivotal role in tumor immune evasion, inflammatory responses, and therapy resistance through bidirectional crosstalk with the cGAS-STING pathway (Fig. 6). For instance, IL-6, a key regulatory hub, is both driven by cGAS-STING signaling and reciprocally modulates its function. Al-Asmari et al. elucidated the intricate relationship between the cGAS-STING pathway and IL-6 expression. They discovered that STING is a

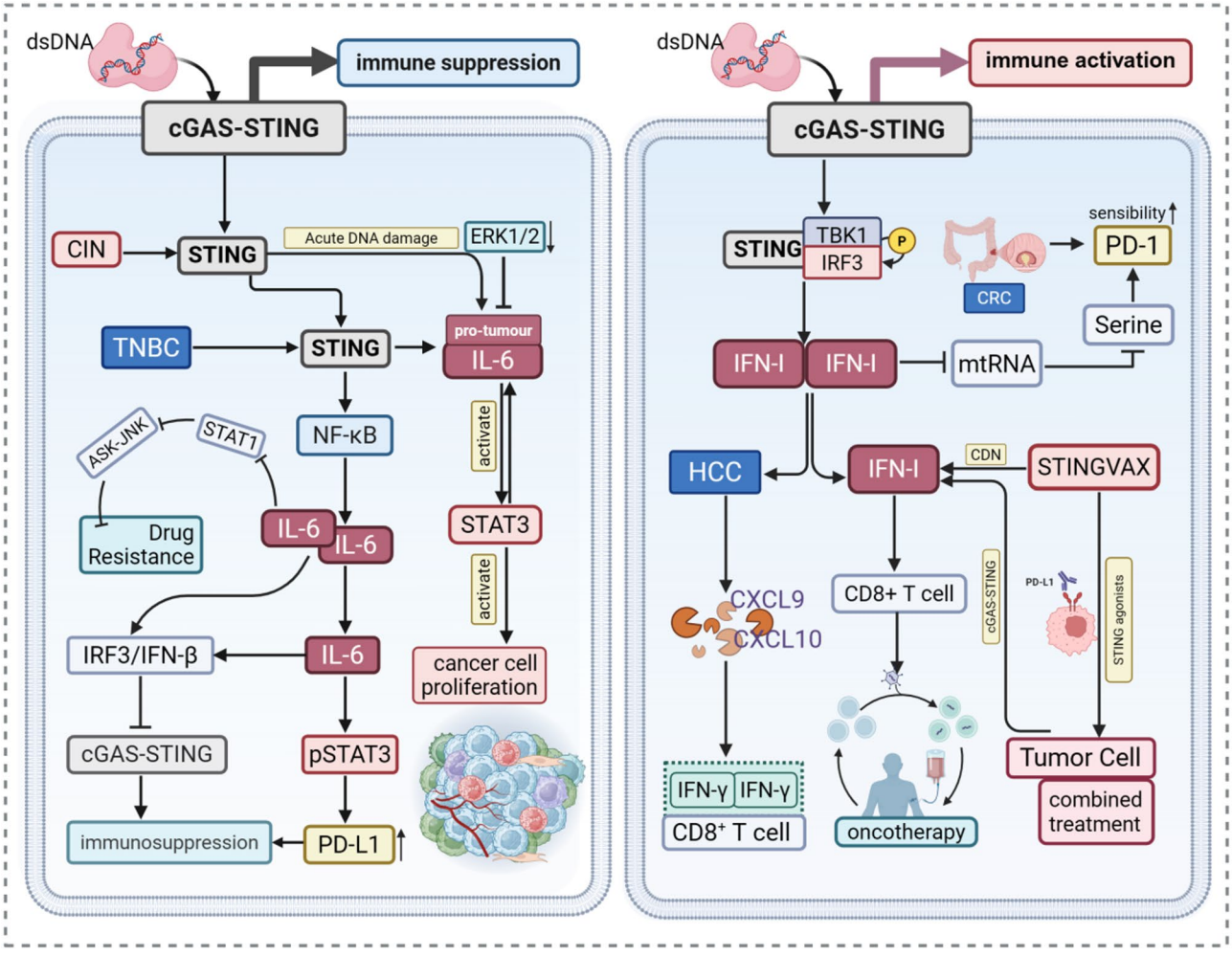

Fig. 6 Interactions and regulatory mechanisms between the cGAS-STING pathway and other components within the TIME. The interaction between the cGAS-STING pathway and IL-6 forms an immunosuppressive network: STING activation promotes IL-6 expression via the NF-κB-STAT3 axis. IL-6 subsequently enhances tumor cell survival, PD-L1 upregulation, and therapeutic resistance, while concurrently inhibiting the anti-tumor effects mediated by the IRF3/IFN-β pathway, thus acting as an "immune brake". Furthermore, cGAS-STING signaling, mediated by IFN-I, regulates the spatiotemporal expression of CXCL9/10, reshaping the immune microenvironment to enhance T cell infiltration and effector functions. Targeted interventions within this network (such as combining STING agonists with IL-6 inhibitors or PD-1 blockade) can overcome immunosuppression and synergistically enhance antitumor efficacy. The diagram integrates key nodes, including costimulatory factors and immune checkpoints, illustrating the translational significance of IL-6 and IFN-I functioning respectively as bidirectional switches for "immune suppression" and "immune activation"

major contributor to the rapid production of pro-tumorigenic IL-6 in cancer cells following DNA damage. In turn, this IL-6 leads to autocrine and paracrine activation of STAT3 signaling, further promoting cancer cell survival under conditions of DNA damage and exposure to pro-apoptotic mediators such as TNF-α [125]. Another study revealed that STING-mediated NF-κB activation in triple-negative breast cancer induces IL-6 expression and pSTAT3 activation, enhancing cell survival and PD-L1 upregulation, thereby fostering immune suppression [126]. Additionally, chromosomal instability has been shown to stimulate cGAS-STING-dependent IL-6 production, where elevated IL-6 and NF-κB counteract STAT1- and ASK-JNK-mediated cell death, promoting tumor survival and therapy resistance [127]. Notably, IL-6 can suppress the IRF3/IFN-β arm of the cGAS-STING pathway, establishing a self-limiting immunosuppressive loop that attenuates antitumor immunity [127]. Thus, targeting IL-6-mediated cGAS-STING signaling may represent a viable therapeutic strategy [128].

Unlike IL-6, which promotes tumor progression, the production of IFN-I is typically induced by the cGAS-STING pathway and tends to inhibit tumor advancement [129]. Research has shown that in colorectal cancer cells, cGAS-STING signaling drives the secretion of IFN-I, which, by depleting mtDNA or blocking its release, limits the immune stimulation and tumor-suppressive effects of serine deprivation, thereby enhancing the tumor's sensitivity to targeted PD-1 immune checkpoint inhibitors [130]. In the field of translational medicine, the development of the STINGVAX vaccine exemplifies the therapeutic potential of this pathway. By utilizing a delivery system that encapsulates CDN, the vaccine can induce upregulation of PD-L1 expression in tumor cells, creating a synergistic effect for combination therapy with anti-PD-1 treatment, particularly for patients resistant to immune checkpoint inhibitors [131]. Furthermore, IFN-I plays a central bridging role between STING signaling and $CD8^+$ T cell immunity. Notably, in the bone tumor microenvironment, STING-mediated IFN-I signaling has dual clinical value: it enhances the infiltration of $CD8^+$ T cells into the bone marrow to boost anti-tumor responses while also significantly alleviating cancer pain through neuroimmune modulation, achieving a synergistic effect between anti-tumor activity and symptom management [132].

Additionally, IFN-I drives the secretion of various chemokines, particularly CXCL9 and CXCL10, which are crucial for the migration and infiltration of $CD8^+$ T lymphocytes [133]. In hepatocellular carcinoma, STING activation can reprogram the immune microenvironment in distant tumors, triggering the release of IFN-I and chemokines (CXCL9 and CXCL10), thereby amplifying T cell responses to tumor neoantigens [134]. Jiang and colleagues applied the regulation of CXCL9 expression via the aforementioned pathway in tumor therapy, successfully upregulating CXCL9 expression in myeloid cells through intratumoral administration of STING-activated nanovaccines, which recruited $CD8^+$ T cells expressing IFN-γ in peripheral blood. In turn, IFN-γ stimulated CXCL9 expression in myeloid cells. The positive feedback loop between CXCL9 and T cell-derived IFN-γ enhanced T cell-mediated immune responses, improving anti-tumor efficacy [135]. Further studies have indicated that downregulation of the cGAS-STING pathway reduces the expression of IFN-I downstream genes such as CXCL9 and CXCL10, inhibiting the activation of immune cells in the TIME and consequently increasing the immune evasion capabilities of cancer cells [136].

In summary, the cGAS-STING pathway and its interaction network with soluble mediators constitute a bidirectional regulatory switch for TIME, with IL-6 and IFN-I acting as "immune brakes" and "immune accelerators" respectively. The balance between these factors influences tumor progression and treatment response. By elucidating the spatiotemporal dynamics of these molecules, precise combination strategies can be designed to transform an immunosuppressive microenvironment into a therapeutic advantage.

Translational medicine perspective: clinical strategies and combination applications of cGAS-STING targeted therapy

In the context of malignant transformation or treatment, the recognition of misplaced and abnormal DNA is fundamental to cGAS activation. As previously outlined, we discussed the accumulation of intrinsic DNA within tumor cells and the subsequent activation of cGAS. We then explored how the second messenger cGAMP, catalyzed by cGAS, is transmitted between cells to collaboratively regulate the biological processes of STING-dependent signaling networks in innate immune cells and stromal cells within the TIME [6]. Notably, the accumulation of mutations in cancer cells not only induces malignant transformation but also activates the host's anti-tumor immune response. Numerous studies targeting the cGAS-STING pathway, particularly therapeutic strategies aimed at TIME, provide compelling evidence for this phenomenon [137]. Currently, clinical translation targeting the cGAS-STING pathway primarily focuses on two major directions: first, developing agonists that directly target the pathway as novel immunotherapeutic monotherapies; and second, utilizing cGAS-STING activators as immune-sensitizing agents in combination with cancer vaccines, immune checkpoint inhibitors, CAR-T cell therapy, and other approaches. This combination strategy aims to significantly improve the response rates of existing therapies by remodeling the TIME [138].

The following sections will briefly elaborate on the core mechanisms and clinical progress of these strategies.

Drug development targeting the cGAS-STING pathway

Targeting cGAS

Mn^{2+}

Mn^{2+} is a potent activator of cGAS, capable of inducing IFN-I and cytokine production in cells even in the absence of infection [139]. Previous studies revealed that Mn^{2+} is released from mitochondria and the Golgi apparatus during viral infection, accumulates in the cytoplasm, and subsequently binds to cGAS, enhancing its sensitivity to dsDNA and enzymatic activity [140]. Currently, multiple anticancer therapies leveraging Mn^{2+}-mediated activation of the cGAS-STING pathway have been developed [141]. For instance, Mn^{2+} significantly enhances the cytotoxic functions of $CD8^+$ T cells and NK cells in a cGAS-STING-dependent manner, promotes macrophage polarization toward the M_1 phenotype, and improves antigen presentation efficiency [141]. Additionally, Mn^{2+} remodels the immunosuppressive tumor microenvironment, increasing tumor infiltration of cytotoxic T lymphocytes (CTLs) and fostering more robust antitumor immune responses [142]. Recent studies have also uncovered molecular links between Mn^{2+}-regulated pathways and ferroptosis. In colon cancer cells, Mn^{2+}-activated cGAS-STING signaling induces IFN-I production while downregulating dihydroxyacid dehydratase expression, leading to abnormal accumulation of lipid peroxides and ROS, ultimately triggering ferroptosis via an iron-dependent mechanism [143]. This dual mechanism of action, which both activates innate immune responses and induces tumor-specific cell death, indicates that Mn^{2+} has excellent potential in anti-tumor therapy and helps to develop new anti-tumor treatment strategies.

NanoISD

Targeting the cGAS-STING pathway with interferon-stimulatory DNA (ISD) represents a highly promising strategy in cancer immunotherapy. However, its clinical application faces limitations due to challenges such as nuclease degradation, low cellular uptake efficiency, and inefficient cytosolic delivery [144]. To overcome these barriers, the team led by Kyle M. Garland developed a nucleic acid-based immunotherapeutic agent called NanoISD. NanoISD is a nanoparticle formulation specifically designed to target cGAS, engineered with deoxyribonuclease resistance to prevent enzymatic degradation and facilitate ISD release from endosomes into the cytosol, thereby potently activating the cGAS-STING pathway. Preclinical studies have shown that intratumoral injection of NanoISD significantly enhances pro-inflammatory cytokine production within the TIME and promotes the infiltration of NK cells and T lymphocytes [145]. This precise immunomodulatory effect not only demonstrates the therapeutic potential of NanoISD as a novel immune stimulator but also addresses the dosing challenges of STING agonists through the targeted delivery capability of nanocarriers.

Targeting cGAMP

ENPP1, a key phosphodiesterase regulating the cGAS-STING signaling pathway, suppresses innate immune activation by degrading the second messenger cGAMP, thereby impairing antitumor immune responses [146]. Its tumor-promoting role has been validated across multiple animal models, including breast cancer where ENPP1 overexpression significantly enhances bone metastasis [147]. Consequently, ENPP1 inhibitors have emerged as novel cGAS-STING pathway agonists [148, 149]. In preclinical studies, MV-626—a highly selective ENPP1 inhibitor—demonstrated durable antitumor immunity upon intraperitoneal monotherapy in Panc02-SIY pancreatic cancer models, with radiotherapy combination further extending mouse survival [150]. Additional ENPP1 inhibitors like SR-8314 and SR-8291 increased tumor-infiltrating $CD8^+/CD4^+$ T cell ratios while reducing immunosuppressive TAMs [151]. Clinically, RBS-2418—the first ENPP1 inhibitor entering Phase 1a/b trials (NCT05270213, NCT05683470)—exhibited favorable oral bioavailability and safety profiles in monotherapy and pembrolizumab combination, with no dose-limiting toxicities observed. These advancements establish ENPP1 inhibition as a promising clinical strategy for cancer immunotherapy.

Targeting STING

As of now, agonists targeting the STING pathway can be categorized into three main classes: CDNs and their derivatives, 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and its analogs, and novel small-molecule agonists.

CDNs and their derivatives

CDNs derived from bacteria are natural agonists of the cGAS-STING pathway, effectively activating the innate immune system. Various CDNs molecules, such as cyclic di-GMP (c-di-GMP), cyclic di-AMP (c-di-AMP), and cGAMP, play crucial roles in regulating immune responses and inhibiting tumor proliferation [152]. For instance, in murine metastatic breast cancer models, low-dose c-di-GMP enhances $CD8^+$ T cell-mediated tumor antigen recognition by inducing the MDSCs to secrete IL-12, while high doses directly activate caspase-3 to trigger cancer cell apoptosis [153]. Additionally, c-di-AMP has a unique mechanism in regulating the

cGAS-STING pathway; it can activate IFN-I in cancer cells, induce the translocation of IRF-3 to the mitochondria, and initiate caspase-9-mediated apoptosis in tumor cells [154]. Furthermore, c-di-AMP can induce high levels of antigen-specific immunoglobulin G (IgG) antibodies and Th1/CTL immune responses [155]. On the other hand, 2′,3′-cGAMP serves as a second messenger for STING signaling in mammalian cells and demonstrates remarkable anti-tumor effects. In mouse CT26 colon adenocarcinoma cells, cGAMP inhibited tumor growth and significantly extended survival by activating STING and its downstream STING-IRF3 signaling pathway [156]. Moreover, intratumoral injection of 2′,3′-cGAMP in the B16F10 mouse model significantly reduced lung metastasis [157].

Despite the significant immunomodulatory and antitumor activities of natural CDNs, their clinical application is limited by stability and delivery efficiency issues. To overcome these limitations, researchers have developed more effective synthetic CDNs [152]. Among these, ADU-S100 is the first synthetic CDN to enter clinical trials for cancer immunotherapy. Compared to other CDNs, ADU-S100 exhibits higher stability and lipophilicity [158]. Preclinical studies using a variety of mouse tumor models have shown that intratumoral injection of ADU-S100 can induce tumor-specific $CD8^+$ T cell responses, demonstrating exceptional anti-tumor efficacy [159, 160]. In a Phase 1 dose-escalation clinical trial involving patients with advanced/metastatic solid tumors or lymphomas (NCT02675439), the safety of ADU-S100 as a monotherapy was evaluated, and no dose-limiting toxicities were reported in the 40 patients involved [161]. However, the clinical trial of ADU-S100 in combination with pembrolizumab for patients with PD-L1-positive recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) has been terminated (NCT03937141), and related data have not yet been published. IACS-8803 and IACS-8779 are two additional 2′,3′-thio-phosphate CDNs analogs that have shown more pronounced systemic anti-tumor responses than ADU-S100 in the B16 melanoma mouse model [162]. Other STING agonists, such as MK-1454, are another synthetic CDNs entering clinical development, where partial remission of tumor lesions has been observed in patients with HNSCC, and are currently in Phase II clinical trials [163]. Notably, Dae-Shik Kim and colleagues have developed a synthetic CDN drug, E7766, which exhibits broad-spectrum antitumor activity and has been shown in animal studies to induce tumor-specific immune memory, demonstrating promising anti-tumor potential [164]. E7766 is currently being evaluated in a Phase 1/1b clinical trial as a monotherapy for patients with advanced solid tumors or lymphomas (NCT04144140), and its clinical efficacy and safety are under close scrutiny. Additionally, several other CDNs derivatives, including BMS-986,301, BI1387446, and SB11285, are currently undergoing Phase 1 clinical studies.

In summary, synthetic CDNs as STING agonists have demonstrated potent anti-tumor activity, with numerous related clinical trials ongoing or completed. As the performance of CDNs continues to improve and delivery technologies advance, synthetic CDNs are expected to exhibit enhanced clinical potential in clinical applications.

DMXAA and its analogs

DMXAA is the first STING agonist to enter oncology clinical trials and remains the only drug to have progressed to Phase III. Originally designed as an anti-angiogenic agent, subsequent studies revealed its direct interaction with STING and demonstrated significant anticancer potential [165, 166]. First, DMXAA induces apoptosis in tumor endothelial cells, irreversibly disrupting established tumor vasculature [95]. Second, it activates the innate immune system by inducing inflammatory cytokine production, with clinical trials showing promising results in selected melanoma and squamous cell carcinoma patients [167]. Moreover, DMXAA counteracts immune escape by disseminated cancer cells. In acute myeloid leukemia (AML) models, intravenous DMXAA administration directly activates STING, triggering IFN-I release, enhancing host DC and T cell activity, and thereby sustaining immune memory to improve survival rates in leukemic mice [168]. Critically, DMXAA reprograms the TIME by repolarizing bone marrow-derived M_2 macrophages into antitumor M_1 phenotypes and inducing key effector molecules (such as ISGs, IFN-β, IFN-γ, TNFα) in T cells, which activate stress-response and pro-death pathways [169, 170].

Despite robust preclinical data, DMXAA failed to meet efficacy endpoints in a Phase III trial for NSCLC [171, 172]. Translational studies identified the root cause: DMXAA's activation efficacy for human STING (hSTING) is 100-fold lower than for murine STING (mSTING). This species-specific disparity in STING binding explains the disconnect between preclinical success and clinical outcomes, highlighting the need for humanized models to validate target engagement in preclinical research [172].

To address this limitation, researchers are developing DMXAA analogs with higher hSTING affinity. Zhang Yibo and colleagues designed α-mangostin, a xanthone-derived analog, which activates hSTING more potently than mSTING [173]. Similarly, the human-selective analog 8-MeXAA suppresses tumor growth by stimulating IL-6 and IL-8 production in leukocytes [174]. These findings not only inform the rational design of STING

agonists but also advance the development of novel therapies for future clinical trials.

Novel small-molecule agonists

The development of novel small-molecule STING agonists has expanded the chemical space of agonists, providing more options for clinical development. Among them, Amide-Benzimidazole (ABZI) drugs represent a breakthrough in STING agonists for cancer immunotherapy [175]. These agonists exhibit significantly enhanced binding affinity through 4-carbon butane linker dimerization [176]. In immunocompetent mice with established syngeneic colon tumors, intravenous administration of diABZI (1.5 mg/kg) resulted in nearly 80% of treated animals achieving complete tumor regression by study endpoint [175]. Meanwhile, the oral non-nucleotide hSTING agonist MSA-2 from Merck has garnered significant attention due to its unique administration route. In murine tumor models, MSA-2's responsiveness to the acidic tumor microenvironment markedly enhances drug tolerability [177]. Furthermore, MSA-2 demonstrates potential long-term therapeutic efficacy in cervical cancer treatment [178]. Notably, Bryan Gall discovered compound C11 through high-throughput screening, which for the first time revealed that STING agonists activate antiviral responses through an IFN-dependent pathway and synergistically enhance anti-tumor immune effects, providing a novel combination strategy for the immunotherapy of pathogen-associated tumors (such as HPV^+ cervical cancer) [179]. In addition, small-molecule STING agonists such as SR-717, ALG-031048, TTI-10,001, and MK-2118 are continuously being designed and developed, aiming to provide a stronger theoretical basis and more treatment options for cancer therapy [180, 181].

We have observed that current clinical research targeting the cGAS-STING pathway exhibits a preference for specific targets, with over 80% of candidate drugs entering clinical trials being STING agonists (such as DMXAA analogs and diABZI), while candidates targeting cGAS or cGAMP are primarily in the preclinical development stage. This differentiation is mainly due to the differences in target characteristics and translational challenges: as the terminal effector of the pathway, STING has a well-defined structural activation mechanism that provides a clear path for small molecule drug design, and intratumoral injection can circumvent systemic toxicity [182]. In contrast, the catalytic activity of cGAS is regulated by a multi-layered balance of intracellular DNA/Mn^{2+} dynamics, making drug development more challenging due to complex allosteric mechanisms, while the water solubility of cGAMP and its rapid degradation mediated by ENPP1 lead to low intracellular delivery efficiency. Despite this, existing preclinical models may overestimate the cross-species translational potential of STING agonists due to the differences in ligand binding between hSTING and mSTING (for example, the species-specific failure of DMXAA in humans). On the other hand, strategies targeting upstream cGAS/cGAMP demonstrate more broadly applicable clinical value due to the evolutionary conservation of the pathway. Below, we summarize the research progress and clinical translation strategies for agonists targeting various points in this pathway (Table 1).

Combination of cGAS-STING agonists and other therapies

Combination with conventional therapies

Chemotherapy and radiotherapy remain the most conventional methods for eliminating tumors. Several previous studies have indicated that, although these treatments do not directly target the cGAS-STING pathway, they can activate the cGAS-STING axis in a "circuitous" manner, enhancing anti-tumor immune responses and reducing side effects induced by classical therapies (Table 2) [183, 184]. For example, in the context of radiotherapy for lung metastases, inhalation of phosphatidylserine-coated nanoliposomes loaded with cGAMP (NP-cGAMP) has been shown to achieve targeted pulmonary delivery of a STING agonist. This approach rapidly delivers NP-cGAMP to the lungs, stimulating STING signaling in antigen-presenting cells (APCs), promoting IFN-I production. The combination of NP-cGAMP and fractionated ionizing radiation (8Gy×3) effectively inhibits tumor metastasis in the irradiated target area and significantly reduces metastasis in unirradiated lung regions [185]. Similarly, in colon cancer tumors, intratumoral injection of 2'3'-cGAMP (10 μg) significantly enhanced the anti-tumor efficacy of local radiotherapy (20 Gy) in a STING-dependent manner [184]. Studies in pancreatic cancer have further validated this synergistic effect, demonstrating that the combination of radiotherapy (10 Gy) and the STING agonist RR-S2-CDG (10 μg) breaks down the tumor immune-tolerant microenvironment, enhancing the T cell immune responses required to control local tumor growth and distant metastasis [186]. Regarding chemotherapy, chemotherapeutic agents can induce DNA damage, thereby activating the cGAS-STING pathway to enhance DC-mediated antigen presentation and T cell responses [10]. Furthermore, studies have reported that the combination of cisplatin and IFN is more effective at inhibiting tumor growth and prolonging median survival in mice compared to cisplatin alone [187]. In addition, in terms of alleviating the side effects of chemotherapy, the combination of STING agonist cGAMP and 5-fluorouracil (5-FU) in CT26 mouse colon cancer model can delay tumor progression and reduce intestinal side effects such as nausea, vomiting and hematochezae caused by 5-FU [156].

Table 1 Research and development progress of cGAS-STING pathway agonists and clinical transformation strategies

Drug candidate /strategy	Type	Cancer type	Phase	Clinical trial number /status
Mn^{2+}	cGAS agonists	Colon Cancer, Melanoma	Pre-clinical	Animal model validation
NanoISD	cGAS agonists	Solid Tumors	Pre-clinical	Animal model validation
MV-626	ENPP1 inhibitor	Pancreatic Cancer	Pre-clinical	SITC 2018 P410(Conference)
SR8541A	ENPP1 inhibitor	Solid Tumors	Phase1	NCT06063681
RBS-2418	ENPP1 inhibitor	Advanced, Metastatic, and Progressive Colorectal Cancer	Phase2a	NCT06824064
RBS-2418	ENPP1 inhibitor	Advanced, Metastatic Solid Tumors	Phase1a/b	NCT05270213
DMXAA	DMXAA and its analogues	Solid Tumors	Phase1	NCT00863733
DMXAA(ASA404)	DMXAA and its analogues	Refractory Tumors	Phase1	NCT00856336
DMXAA(ASA404)	DMXAA and its analogues	Advanced Solid Tumors or Lymphomas	Phase1	NCT01299701
DMXAA(ASA404)	DMXAA and its analogues	Solid Tumors	Phase1	NCT00003697
DMXAA(ASA404)	DMXAA and its analogues	Adult Advanced Cancer	Phase1	NCT01278758
DMXAA(ASA404)	DMXAA and its analogues	Adult Cancer Patients With Impaired Hepatic Function	Phase1	NCT01278849
KL340399	Synthetic CDN agonists	Advanced Solid Tumors	Phase1	NCT05549804
KL340399	Synthetic CDN agonists	Advanced Solid Tumors	Phase1	NCT05387928
ADU-S100	Synthetic CDN agonists	Advanced、Metastatic Solid Tumors or Lymphomas	Phase1	NCT02675439
MK-1454	Synthetic CDN agonists	Advanced、Metastatic Solid Tumors or Lymphomas	Phase1	NCT03010176
E7766	Synthetic CDN agonists	Advanced Solid Tumors or Lymphomas	Phase1/1b	NCT04144140
CRD3874-SI	Novel STING agonists	AML	Phase1	NCT06626633
VAX014	Novel STING agonists	Advanced Solid Tumors	Phase1	NCT05901285
SB11285	Novel STING agonists	Advanced Solid Tumors	Phase1	AACR 2017 P-A25(Conference)
CRD3874-SI	Novel STING agonists	Solid Tumors	Phase1	NCT06021626

Combination with cancer vaccines

In addition to classical therapies, preclinical data have reported the combined use of STING agonists with cancer vaccines, which can significantly enhance anti-tumor immune responses and overcome the limitations of traditional therapies [188]. The core advantage of this combination therapy lies in its dual mechanism of activating the innate immune pathway (the cGAS-STING pathway) and the adaptive immune response (vaccine antigen presentation), thereby systematically reshaping the TIME to more effectively initiate and enhance T cell-mediated specific anti-tumor immunity. For example, the combination of ADU-S100 and chimeric peptide vaccines [70], as well as c-di-GMP and Listeria vaccines [153], have both shown synergistic effects, effectively inhibiting tumor growth and metastasis. Moreover, in a notable innovation, Fu Juan and his colleagues developed the first STING-based cancer vaccine, STINGVAX, which, when administered in conjunction with a PD-1 inhibitor (200 μg via intraperitoneal injection, twice a week), promoted the regression of low-immunogenic tumors that were unresponsive to monotherapy with the PD-1 inhibitor [131]. Recently, an effective STING-dependent lipid nanoparticle (LNP) also has been developed as an adjuvant for the delivery of antigen-specific mRNA vaccines, showing significant survival advantages in clinical applications [189]. These studies collectively reveal the tremendous potential of STING agonists as adjuvants for cancer vaccines, particularly in enhancing vaccine immunogenicity, increasing immune infiltration in the microenvironment, and overcoming resistance to PD-1 inhibitors. In the future, with the development of more novel STING agonists and delivery systems, as well as a deeper understanding of the mechanisms of combination therapies, combined cancer vaccine therapies are expected to play a greater role in the field of tumor treatment.

Combination with immune checkpoint inhibitors

In tumor immunotherapy, the synergistic strategy of combining STING agonists with immune checkpoint inhibitors (ICIs) provides a breakthrough approach to overcoming the limitations of "cold tumors". This strategy activates and reshapes the TIME through the cGAS-STING pathway, creating the necessary conditions for the efficacy of ICIs [138]. Pre-existing T cell infiltration is a key prerequisite for the response to ICIs, and the activation of STING significantly enhances the directional migration of DCs and T cells to the tumor by upregulating Th1 chemokines (such as CXCL9/10), thereby transforming "cold tumors" into "hot tumors" [10, 190]. This mechanism not only provides an upstream driving force for antigen presentation and T cell activation for PD-1 inhibitors but also further amplifies the targeted effects of ICIs by inducing the upregulation of PD-L1 expression [191]. For example, in a Phase 1b multicenter study, the combination of ADU-S100 with a PD-1 inhibitor significantly improved the response rate. When $PD\text{-}L1^{low}$ mouse tumor cells were infected with a cGAS-STING-encoding adenovirus, nearly all infected tumor cells expressed PD-L1, whereas only 46% of tumor cells in the

Table 2 Clinical strategies for the combination of cGAS-STING pathway agonists and other drugs

cGAS-STING drug	combination drug	Targets	Cancer type	Phase	NCT number
ONM-501	cemiplimab	STING	Advanced solid tumors and lymphomas	Phase1	NCT06022029
STING-dependent Adjuvants (STAVs)	dendritic cell (DC) vaccine therapies	STING	Aggressive Relapsed/Refractory Leukemias	Phase1	NCT05321940
IMSA101	PULSAR radiotherapy	STING	Metastatic Kidney Cancer	Phase2	NCT06601296
IMSA101	PULSAR-ICI	STING	Oligoprogressive Solid Tumor Malignancies	Phase2	NCT05846659
IMSA101	PULSAR-ICI	STING	Oligometastatic NSCLC and RCC	Phase2	NCT05846646
MIW815(ADU-S100)	PDR001	STING	Advanced/Metastatic Solid Tumors or Lymphomas	Phase1	NCT03172936
MIW815(ADU-S100)	Pembrolizumab	STING	Head and Neck Cancer	Phase2	NCT03937141
GSK3745417	dostarlimab	STING	Advanced solid tumors	Phase1	NCT03843359
SNX281	pembrolizumab	STING	Advanced solid tumors and lymphomas	Phase1	NCT04609579
TAK-500	Pembrolizumab	STING	Select Locally Advanced or Metastatic Solid Tumors	Phase1/2	NCT05070247
Dazostinag(TAK-676)	pembrolizumab	STING	Adults With Advanced or Metastatic Solid Tumors	Phase1/2	NCT04420884
MK-2118	Pembrolizumab	STING	Adults With Advanced/Metastatic Solid Tumors or Lymphomas	Phase1	NCT03249792
TAK-676	Pembrolizumab	STING	non-small-cell lung cancer (NSCLC), triple-negative breast cancer (TNBC) and squamous-cell carcinoma of the head and neck (SCCHN)	Phase1	NCT04879849
DMXAA(ASA404)	carboplatin and paclitaxel	STING partial agonist	Advanced Non-Small Cell Lung Cancer	Phase1/2	NCT00832494
DMXAA(ASA404)	Carboplatin/Paclitaxel/ Cetuximab	STING partial agonist	Refractory Solid Tumors	Phase1	NCT01031212
DMXAA(ASA404)	Alone or in Combination With Taxane-based Chemotherapies	STING partial agonist	Advanced Solid Tumor	Phase1	NCT01290380
DMXAA(ASA404)	Docetaxel	STING partial agonist	Hormone Refractory Metastatic Prostate Cancer	Phase2	NCT00111618
DMXAA(ASA404)	Docetaxel	STING partial agonist	Solid Tumors	Phase1	NCT01285453
DMXAA(ASA404)	Paclitaxel Plus Carboplatin Regimen or Docetaxel	STING partial agonist	Advanced Cancer	Phase1	NCT01240642
DMXAA(ASA404)	Paclitaxel and Carboplatin	STING partial agonist	Non-Small Cell Lung Cancer	Phase1	NCT00674102
DMXAA(ASA404)	Docetaxel	STING partial agonist	Advanced Urothelial Carcinoma	Phase2	NCT01071928
DMXAA(ASA404)	Paclitaxel, Carboplatin	STING partial agonist	Extensive-Stage Small Cell Lung Cancer	Phase2	NCT01057342
DMXAA(ASA404)	Docetaxel	STING partial agonist	(Stage IIIb/IV) Non-small Cell Lung Cancer	Phase3	NCT00738387
DMXAA(ASA404)	Paclitaxel and Carboplatin	STING partial agonist	Stage IIIb/IV Non-Small Cell Lung Cancer	Phase3	NCT00662597

control group expressed PD-L1. The underlying biological rationale here is the synergistic amplification of T cell infiltration mediated by STING in conjunction with the PD-1 inhibitor [192]. Similarly, when cGAMP (1–10 μg) was delivered via intramuscular injection to B16 melanoma mice, it significantly enhanced the anti-tumor effects of PD-L1 inhibitors and improved the survival rates of tumor-bearing mice [193].

It is noteworthy that this synergistic effect is not limited to the PD-1/PD-L1 axis; the integrity of STING signaling is also crucial in CTLA-4 inhibitor therapy. STING-deficient mice showed a significantly reduced tumor clearance rate when treated with a combination of CTLA-4 antibodies and radiotherapy. In a prostate cancer model, a multi-target combination therapy (such as anti-CTLA-4/PD-1/4-1BB antibodies combined with the STING agonist CDG) increased the cure rate from 40 to 75%, further validating the pivotal role of STING in integrating innate and adaptive immune responses [194]. In a model simulating metastatic tumors with flank and tongue tumors, researchers delivered STING agonists to the flank tumor and combined it with systemic treatment using α-PD-1 and α-CTLA-4 antibodies, resulting in sustained tumor regression in 71% of the mice [195]. Therefore, the combination of STING agonists and ICIs effectively enhances anti-tumor efficacy.

Combination with CAR-T cell therapy

CAR-T cell therapy represents one of the most promising anticancer strategies, utilizing genetically engineered T cells expressing chimeric antigen receptors (CARs) to precisely target and eliminate tumor cells [196]. However, the immunosuppressive tumor microenvironment and intratumoral heterogeneity significantly limit the

therapeutic efficacy of CAR-T cells in clinical applications [197]. To address these challenges, novel combinatorial approaches are being actively explored. For instance, studies demonstrate that DMXAA enhances the secretion of chemokines CXCL9/10, which recruit CXCR3-expressing Th/Tc17 CAR-T cells into tumor foci, thereby alleviating immunosuppression and augmenting CAR-T cell expansion [198]. Moreover, in murine pancreatic tumor models, co-delivery of CAR-T cells with the STING agonist cyclic di-GMP was shown to stimulate immune responses, eliminating tumor cells resistant to adoptively transferred lymphocytes while reversing immunosuppressive TME and preventing immune escape [199]. Further research indicates that the IFN secretion mediated by the cGAS-STING pathway may be associated with the prognosis of patients receiving CAR-T treatment. The intrinsic sensitivity of tumor cells to IFN-γ-induced apoptosis is a key factor for the antitumor activity of $CD4^+$ CAR-T cells [200]. It has been reported that IFN-γ produced by CAR-T cells can not only enhance the activity of endogenous T cells and NK cells but also maintain the cytotoxicity of CAR-T cells, thereby supporting the host's CAR-T immune response [201]. These breakthrough achievements not only provide a theoretical basis for the optimization of CAR-T therapy but also point out a new direction for the future development of cancer immunotherapy (Fig. 7).

The betrayal of immune sentinels: decoding the carcinogenic mechanisms of the cGAS-STING pathway and targeted breakthroughs

Undoubtedly, cGAS-STING pathway agonists have demonstrated remarkable potential in antitumor immunity. However, emerging evidence reveals that the cGAS-STING signaling cascade exerts context-dependent dual effects on tumor progression [202]. The dichotomous role of this pathway is intricately linked to the evolving complexity of the TIME, with outcomes shaped by factors such as hypoxia, nutrient availability, and the presence of immune or stromal cells. In certain contexts, the pathway contributes to malignant transformation by fostering an immunosuppressive TIME and facilitating metastasis [203]. For instance, STING activation in human HPV^+ tongue squamous cell carcinoma promotes treg infiltration; these treg cells subsequently secrete IL-10 and IDO to suppress antigen-specific T-cell activity, ultimately driving tumor progression [204]. Additionally, the STING-IL-35 axis in B cells impairs NK cell proliferation and diminishes NK-mediated antitumor responses [42]. This paradoxical duality underscores the necessity for a nuanced understanding of cGAS-STING regulation and function across heterogeneous tumor ecosystems.

It is noteworthy that a paradox is at play here: despite the expectation that activating pathways similar to antiviral defenses would theoretically inhibit cancer cell growth and survival, in tumors characterized by chromosomal instability (CIN), this pathway is instead "hijacked" by cancer cells. In CIN tumors, constitutive (continuously active) cGAS-STING activation may induce pre-existing resistance to STING agonists in cancer cells, as these tumors have evolved strategies to escape the harmful effects of cytoplasmic DNA. Studies have confirmed that the increased expression of target genes of the cGAS-STING and non-canonical NF-κB pathways is closely associated with higher levels of CIN and poor clinical prognosis. Tumor cells with CIN often choose the chronic activation of the innate immune pathway, thereby spreading to distant organs [205]. By using ContactTracing, a novel single-cell RNA sequencing analytical platform, Li's team demonstrated that CIN-driven chronic STING activation suppresses antitumor immunity and enhances metastatic dissemination [206]. Fortunately, this paradox also provides new insights for cancer therapy. The resistance of tumor cells to cGAS activity reveals the potential of STING inhibitors in advanced cancers, such as the recently discovered covalent inhibitors of STING palmitoylation that mitigate metastasis [207]. Indeed, a significant unresolved question is how these cancer cells alter the downstream circuits of STING to mediate metastasis. One hypothesis suggests that this alteration may be related to the precise control of STING expression levels, where an effective anti-tumor response must maintain a delicate balance; exceeding a specific threshold of STING activity may worsen clinical outcomes [208].

In addition to promoting tumor metastasis and CIN, the use of cGAS-STING agonists may also induce a transient systemic inflammatory response akin to a cytokine storm, leading to unexpected immune reactions and flu-like symptoms in patients [209]. Notably, studies have found that non-nucleotide small-molecule STING agonists can have potential toxicity on T cells. Given that T cells express high levels of STING, they are more susceptible to apoptosis induced by STING activation [210]. Furthermore, systemic administration of STING agonists via intravenous or intraperitoneal injection may excessively activate the cGAS-STING pathway, resulting in unnecessary inflammation in normal tissues [211]. Therefore, future efforts should focus on developing cGAS-STING pathway regulators with tissue-targeting properties to minimize adverse effects caused by systemic immune responses [212].

In conclusion, the "betrayal" of the cGAS-STING pathway is actually a microcosm of the game between tumors and host immunity. The core of targeted breakthroughs lies in understanding and reconstructing the biological significance of this pathway at different evolutionary stages. Through precise molecular interventions

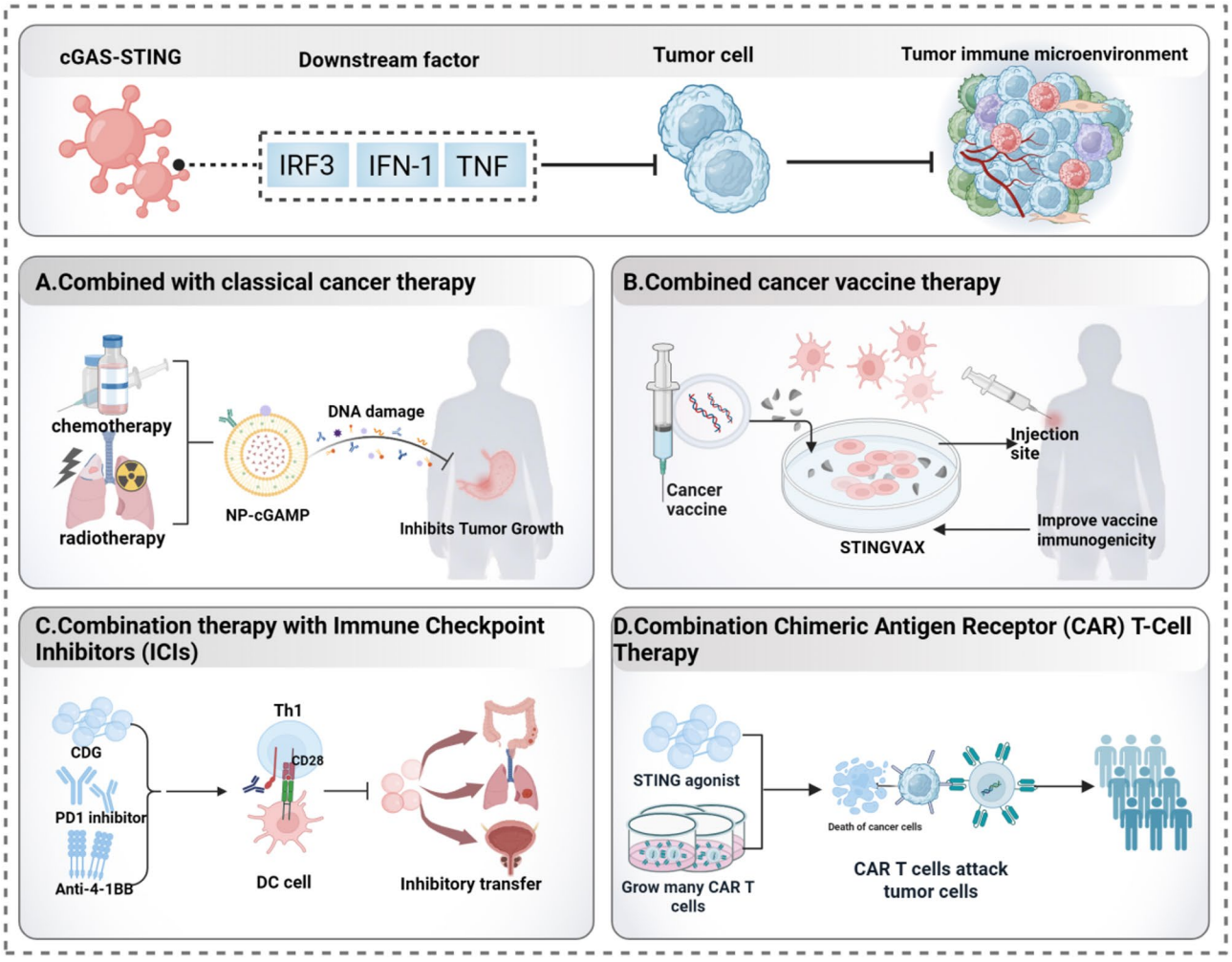

Fig. 7 Synergistic Mechanisms and Translational Potential of cGAS-STING Pathway Combined with Other Therapies. (A) Combination with Conventional Therapies: Radiotherapy and chemotherapy enhance antitumor immunity by indirectly activating the cGAS-STING pathway via DNA damage induction. For instance, radiotherapy combined with STING agonists promotes IFN-I secretion and T cell responses, suppresses metastasis, and mitigates adverse effects; Chemotherapeutic agents (e.g., cisplatin, 5-FU) synergize with STING activation to improve antigen presentation efficiency. (B) Combination with Cancer Vaccines: STING agonists serve as vaccine adjuvants by activating dual innate and adaptive immune responses, reshaping the TIME, enhancing vaccine-primed T cell infiltration, and overcoming resistance to PD-1 inhibitors. (C) Combination with ICIs: cGAS-STING signaling converts "cold tumors" into "hot tumors" by upregulating CXCL9/10 and PD-L1 expression, thereby promoting T cell infiltration and synergizing with PD-1/CTLA-4 inhibitors to amplify therapeutic efficacy. (D) Combination with CAR-T cell Therapy: STING activation recruits CAR-T cells to tumors via CXCL9/10 secretion, reverses the immunosuppressive microenvironment, and enhances CAR-T cell expansion and cytotoxicity

and dynamic balance at the systemic level, the "immune hijacking" by tumors can be transformed into a breakthrough for immunotherapy.

Summary and prospect

The cGAS-STING pathway, a central nexus bridging innate immunity and the TIME, embodies a dynamic regulatory network that harbors both the promise of activating antitumor immune responses and the peril of fostering immunosuppressive escape. This review systematically elucidates how the cGAS-STING pathway constructs a cascade network of antitumor immunity by driving DC subset differentiation, reshaping T cell stemness, regulating macrophage polarization, and enhancing NK cell cytotoxicity. However, chronic activation of cGAS-STING signaling paradoxically induces IL-6/STAT3 axis-mediated immunosuppression, expands treg/Breg cells populations, and facilitates CAFs protumorigenic transformation, ultimately fostering prometastatic niches. This functional heterogeneity warns us that precise intervention needs to go beyond the limitations of traditional "total activation" strategies and instead focus on the spatio-temporal dynamic balance of signaling thresholds, cell subsets, and microenvironment metabolism.

Currently, breakthroughs in synthetic CDNs and nano-delivery systems in preclinical settings have validated the feasibility of locally activating pathways to reshape "cold tumors". However, the species-specific failure of DMXAA, chronic signal escape driven by CIN, and cytokine storms induced by systemic agonists still expose three major bottlenecks in the translational pathway: species interaction bias, the signal threshold paradox, and the spatiotemporal delivery dilemma. Future research must integrate systems biology and synthetic immunology approaches to decode multidimensional regulatory networks, including epigenetic modifications (such as competitive activation of IRF3/NF-κB), metabolic reprogramming (mtDNA leakage-ferroptosis interplay), and phase separation mechanisms. These insights will guide the development of pH-responsive nanoparticles or engineered MSCs for spatiotemporally controlled STING agonist release, the design of multi-omics-guided combination strategies (STING agonists with epigenetic drugs and metabolic modulators), and the exploration of palmitoylation inhibitors or CRISPR-based systems to reverse pro-tumorigenic phenotypes in metastatic tumors. Only by embedding an "ecological regulation" mindset throughout the continuum from basic research to clinical translation can we unravel the intricate interplay between tumors and immunity, thereby opening a new era in cancer immunotherapy through precise decoding of the cGAS-STING pathway.

Abbreviations

ABZI	Amide-Benzimidazole
AML	Acute Myeloid Leukemia
APCs	Antigen-presenting cells
ARF	ADP-ribosylation factor
Breg	Regulatory B cells
BC	Bladder Cancer
CAFs	Cancer-Associated Fibroblasts
CAR-T Therapy	Chimeric Antigen Receptor T-cell Therapy
CDNs	Cyclic dinucleotides
cDC1	Conventional type 1 Dendritic Cell
cDC2	Conventional type 2 Dendritic Cell
c-di-AMP	Cyclic di-AMP
c-di-GMP	Cyclic di-GMP
CIN	Chromosomal instability
COPII	Coat Protein Complex II
CTLs	Cytotoxic T lymphocytes
DAMPs	Damage-Associated Molecular Patterns
DCs	Dendritic Cells
DMXAA	5,6-dimethylxanthenone-4-acetic acid
eEF2K	Eukaryotic elongation factor 2 kinase
ER	Endoplasmic Reticulum
GBM	Glioblastoma
GM-CSF	Granulocyte - Macrophage Colony - Stimulating Factor
HCC	Hepatocellular Carcinoma
hSTING	Human STING
HNSCC	Head and Neck Squamous Cell Carcinoma
ICB	Immune Checkpoint Blockade
ICIs	Immune checkpoint inhibitors
IDO	Indoleamine 2,3-dioxygenase
IFN-I	Type I interferon
IFN-γ	Interferon-gamma
IgG	Antigen-specific immunoglobulin G
IL-6	Interleukin-6
IRF3	Interferon Regulatory Factor 3
IRG1	Immune Response Gene 1
ISD	Interferon-stimulatory DNA
ISG	Interferon-stimulated gene
LLPS	Liquid-liquid phase separation
LPS	Lipopolysaccharide
M_1 TAMs	M_1-polarized Tumor-associated macrophages
M_2 TAMs	M_2-polarized Tumor-associated macrophages
MDSCs	Myeloid-derived suppressor cells
MHC-I	Major Histocompatibility Complex Class I
MHC-II	Major Histocompatibility Complex Class II
MM	Multiple Myeloma
MSCs	Mesenchymal Stem Cells
mSTING	murine STING
mtDNA	mitochondrial DNA
NK cells	Natural Killer cells
NO	Nitric Oxide
NPC	Nasopharyngeal Carcinoma
NTase	Nucleotidyl Transferase
PAMPs	Pathogen-Associated Molecular Patterns
PDAC	Pancreatic Ductal Adenocarcinoma
PRR	Pattern Recognition Receptor
PTMs	Post-Translational Modifications
pDCs	Plasmacytoid Dendritic Cells
ROS	Reactive Oxygen Species
RT	Radiation Therapy
RILI	Radiation-induced lung injury
SIRPα	Signal Regulatory Protein alpha
STIM1	Stromal Interaction Molecule 1
TAA	Tumor-associated antigen
TAMs	Tumor-associated macrophages
TBK1	TANK-binding kinase 1
TGF-β	Transforming Growth Factor-beta
Th1 cell	T helper 1 cell
TIME	Tumor immune microenvironment
TNF	Tumor necrosis factor
TFEB	Transcription Factor EB
Treg cell	Regulatory T cell

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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