Shen *et al. Journal of Hematology & Oncology* (2025) 18:40
https://doi.org/10.1186/s13045-025-01691-5

Journal of Hematology & Oncology

REVIEW Open Access

The cGAS–STING pathway in cancer immunity: mechanisms, challenges, and therapeutic implications

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Abstract

Innate immunity represents the body's first line of defense, effectively countering the invasion of external pathogens. Recent studies have highlighted the crucial role of innate immunity in antitumor defense, beyond its established function in protecting against external pathogen invasion. Enhancing innate immune signaling has emerged as a pivotal strategy in cancer therapy. The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling pathway is a key innate immune signal that activates the immune response and exerts antitumor effects; this is primarily attributed to the DNA receptor function of cGAS, which recognizes exogenous DNA to activate downstream STING signaling. This, in turn, promotes the activation of downstream targets such as IRF-3(Interferon Regulatory Factor 3) and NF-κB, leading to the secretion of type I interferons and proinflammatory cytokines, thereby increasing cellular immune activity. The activation of the cGAS-STING pathway may thus play a crucial role in enhancing anticancer immunity. In this paper, we reviewed the role of cGAS-STING signaling in anticancer immunity and its molecular mechanisms. Additionally, we briefly discuss the current applications of the cGAS-STING pathway in cancer immunity, summarize recent developments in STING agonists, and address the challenges facing the use of the cGAS-STING pathway in cancer therapy. Finally, we provide insights into the role of the cGAS–STING pathway in cancer and propose new directions for cancer immunotherapy.

Keywords Innate immunity, cGAS, STING, Cancer immunity

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Introduction

Cancer continues to be a leading cause of mortality worldwide, with recent studies indicating that approximately one-quarter of all deaths attributable to noncommunicable diseases are due to cancer. Furthermore, both the incidence and mortality rates of cancer have been rising steadily in recent years [1]. Cancer development is a gradual, multistep process in which normal cells undergo mutations that transform them into tumor cells. These cells eventually evade the immune system's antitumor defenses, progressing toward malignancy. The immune system functions as the body's defense mechanism against invading pathogens and abnormal cells and consists of two major branches: innate immunity and adaptive immunity. Innate immunity acts as the first line of defense, preventing pathogen entry through physical barriers, such as the skin and mucosal surfaces, or eliminating pathogens via phagocytic cells. If the innate immune system fails to completely eliminate a pathogen, adaptive immunity is triggered, presenting antigenic peptides and activating immune cells, which subsequently secrete antibodies or cytokines to target and eliminate the pathogen. Tumor cells are typically recognized by the immune system as "nonself" and can be targeted and eliminated by both innate and adaptive immune responses [2]. Additionally, exposed DNA—such as that from phagocytosed pathogens, viral DNA from infections, and DNA released during cellular breakdown—can activate both innate and adaptive immune responses. Exposed DNA or 'nonself' DNA is recognized by specific receptors on the cell membrane or in the cytoplasm, triggering an immune response. These receptors include three main types: Toll-like receptor 9 (TLR9), interferon-inducible protein AIM2 (also known as absent in melanoma 2, AIM2), and cyclic GMP-AMP synthase (cGAS). TLR9 is expressed on the endosomal membrane, where it recognizes extracellular DNA, particularly hypomethylated CpG DNA, and enters the cell through the phagolysosomal system. TLR9 plays a crucial role in defending the body against viral infections and other pathogens. Cytoplasmic double-stranded DNA (dsDNA) activates the AIM2 inflammasome, a caspase-1-activating complex that regulates the production and secretion of proinflammatory cytokines, including IL-1β and IL-18, thereby increasing resistance to DNA viruses and certain cytosolic bacterial pathogens. Cyclic GMP-AMP synthase (cGAS) serves as a key intracellular DNA sensor, and through the activation of the downstream stimulator of interferon genes (STING) pathway, it induces the production of interferons and other antiviral factors, thereby bolstering immune defense against pathogenic threat [3].

cGAS is a double-stranded DNA (dsDNA)-sensitive immunoaccelerator, featuring a highly conserved catalytic domain and two distinct DNA-binding sites at its N- and C-termini [4]. Under normal physiological conditions, DNA is confined to the nucleus of eukaryotic cells, where it effectively segregates from the cytoplasm [4]. However, various stressors—such as endogenous retroviruses, DNA viruses, genomic instability, mitochondrial damage, necrotic cells, or bacterial invasion—can disrupt cellular homeostasis, leading to the accumulation of dsDNA in the cytosol [5–7]. Once present, cytosolic dsDNA interacts with cGAS, forming a 2:2 complex that induces conformational changes, activating cGAS and initiating the synthesis of cyclic GMP-AMP (cGAMP) from ATP and GTP [8]. The synthesized cGAMP, termed "2'3'-cGAMP" owing to its two phosphodiester linkages (2'-5' and 3'-5'), acts as a secondary messenger and induces conformational changes in the STING protein on the endoplasmic reticulum (ER). STING transitions from a dimeric to a tetrameric form and subsequently translocates from the ER to the Golgi apparatus. Upon activation, STING recruits and activates the kinase TBK1, which phosphorylates the interferon regulatory factor 3 (IRF-3) and regulates downstream genes expression [8]. Additionally, activation of STING leads to the recruitment of IKK kinases and the release of NF-κB, which induce the expression of interferons (IFNs) and proinflammatory cytokines, including TNF, IL-1, and IL-6 [8]. Type I IFNs perform diverse immune-stimulating functions, including promoting the maturation, migration, and activation of immune cells such as dendritic cells (DCs), T cells, and natural killer (NK) cells [9]. Once produced, Type I interferons activate the JAK/STAT signaling cascade by binding to interferon receptors on the cell membrane. Phosphorylated STAT1 and STAT2 form the ISGF3 transcriptional complex with interferon regulatory factor 9 (IRF-9), which translocates to the nucleus to initiate the expression of downstream IFN-stimulated genes (ISGs) [10]. This sequence of events creates a positive feedback loop that amplifies IFN production and the release of proinflammatory cytokines. This is the canonical STING activation pathway. In addition, a non-canonical STING activation pathway should be noted. This type of STING activation, following etoposide-induced DNA damage, involves the DNA-binding protein IFI16, along with the DNA damage response factor ATM (ataxia telangiectasia mutated) and PARP-1 (poly-ADP-ribose polymerase 1), leading to the assembly of another STING signaling complex. This complex contains IFI16, the tumor suppressor protein TP53 (also known as p53) and the E3 ubiquitin ligase TRAF6 (tumor necrosis factor receptor-associated factor 6). In this signaling complex, TRAF6 catalyzes the ubiquitination of STING, leading to a major activation of NF-κB, which induces a gene expression program distinct from than induced by the cGAS-STING signaling pathway (Fig. 1) [11].

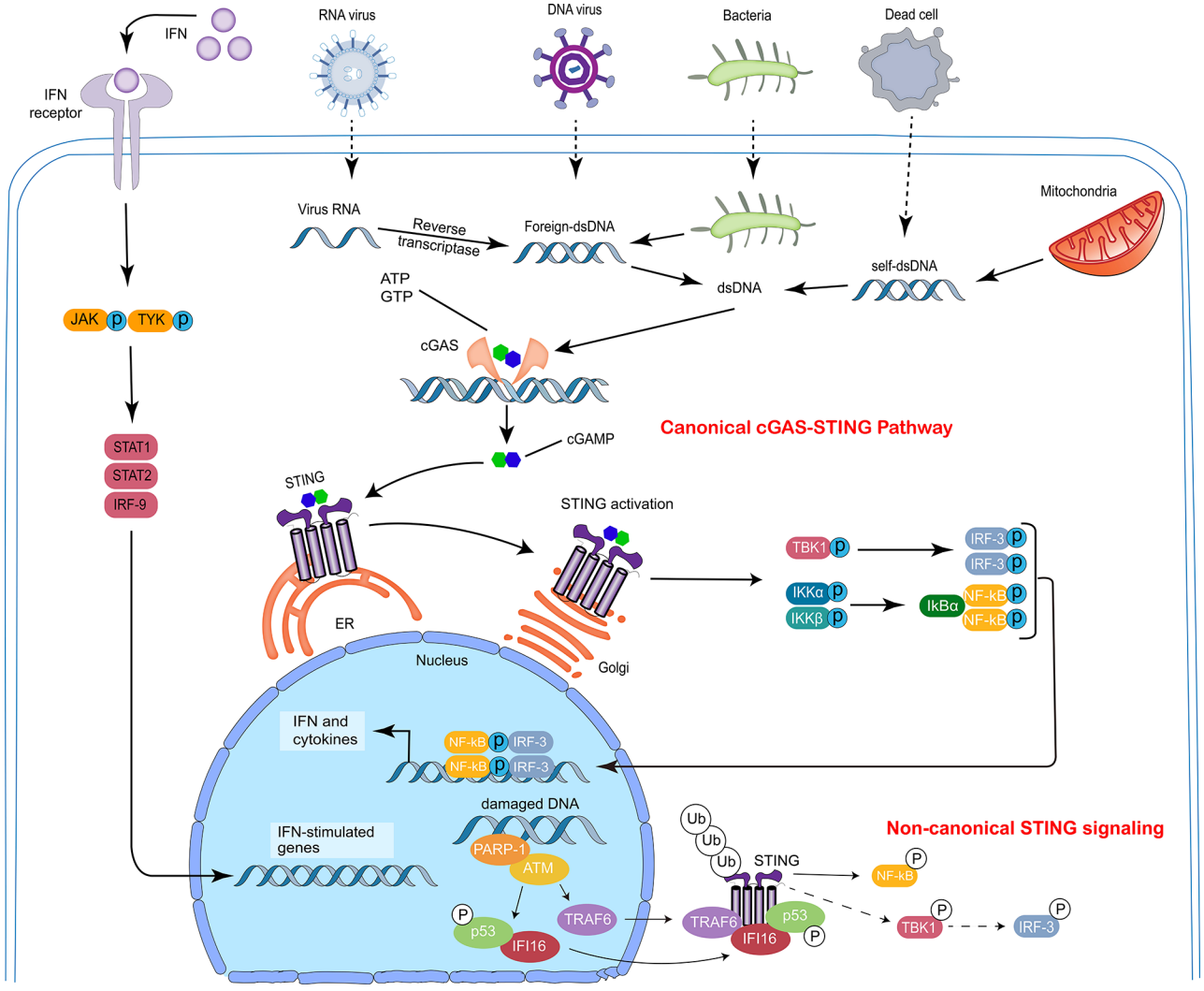

Fig. 1 Schematic of the cGAS–STING pathway. **Canonical cGAS-STING Pathway.** Cytosolic double-stranded DNA (dsDNA), originating from viruses, bacteria, necrotic cells, or other sources, activates cGAS, which catalyzes the synthesis of cGAMP from ATP and GTP. cGAMP subsequently binds to and activates STING, which, upon activation, recruits TBK1 and IKK. This recruitment leads to the phosphorylation of IRF3 and NF-κB, ultimately driving the expression of downstream inflammatory cytokines. **Non-canonical STING Signaling.** Upon DNA damage, ATM and PARP-1 are recruited and promote the assembly of an alternative STING signaling complex comprising IFI16, p53, and the E3 ubiquitin ligase TRAF6. Within this complex, TRAF6 mediates STING ubiquitination, leading to NF-κB activation

The cGAS-STING signaling plays a crucial role in disease progression. In a chronic DIC model, we observed significant activation of the cGAS-STING pathway in cardiac endothelial cells (ECs). This activation leads to reduced NAD^+ levels and subsequent mitochondrial dysfunction through intracellular NADase activity of CD38 [12]. Acquired mutations in STING function can lead to STING-associated vasculopathy in infancy (SAVI), a systemic inflammatory disease characterized by vasculitis and pulmonary fibrosis [13]. The cGAS-STING pathway may also be involved in acute kidney injury (AKI), characterized by renal fibrosis, and in the progression of chronic kidney disease (CKD) [14]. Recent studies have shown that cGAS-STING signaling also plays a crucial role in tumor progression. This pathway regulates tumor cell growth by inducing the expression of downstream target molecules or activating T lymphocytes, thereby enhancing antitumor immunity [15].

In this review, we provide an overview of the role and mechanisms of the cGAS-STING pathway in cancer immunity. We also discuss the current applications of STING signaling in anticancer therapies and recent advancements in STING agonists development and propose future directions for harnessing STING signaling in oncology. The aim of this review is to elucidate the role of the cGAS-STING pathway in cancer and explore new opportunities for its therapeutic application.

The role of cGAS-STING signaling in cancer immunity

The tumor microenvironment (TME) is a complex network that surrounds tumor cells, including the extracellular matrix (ECM), tumor vasculature, fibroblasts, immune cells, and inflammatory cytokines. The TME plays a critical role in tumor progression. cGAS-STING signaling primarily modulates tumor dynamics by regulating immune cells within the TME, thereby influencing the antitumor immune response (Fig. 2). Upon activation, cGAS-STING signaling promotes the maturation of dendritic cells (DCs), increasing their antigen-presenting capabilities. In addition, STING activation facilitates T cell activation and promotes the differentiation of $CD4^+$ T cells. This pathway also induces the expansion of $CD8^+$ T cells and enhances cytokine secretion. Ultimately, STING activation increases chemokine expression, which promotes the infiltration of effector T cells into the tumor and enhances their antitumor efficacy (Fig. 3). In the following sections, we discuss the regulatory role of the cGAS–STING pathway in cancer immunity.

Increased antigen processing and presentation

Dendritic cells (DCs) are the most potent professional antigen-presenting cells (APCs) in the immune system and are known for their exceptional ability to capture, process and present antigens. Upon capturing tumor antigens, dendritic cells (DCs) migrate to the draining lymph nodes, where in conjunction with major histocompatibility complex class I (MHC-I) molecules, they present processed tumor-derived peptides to $CD8^+$ T cells, thereby initiating an adaptive immune response [16, 17]. Tumor cells activate DCs through two primary mechanisms: tumor-derived DNA is phagocytosed by DCs, leading to the activation of the cGAS-STING pathway and the production of type I interferons (IFNs), which promote DC maturation [18, 19], and tumor-derived cyclic GMP-AMP (cGAMP) directly activates the STING pathway and facilitates DC maturation [20].

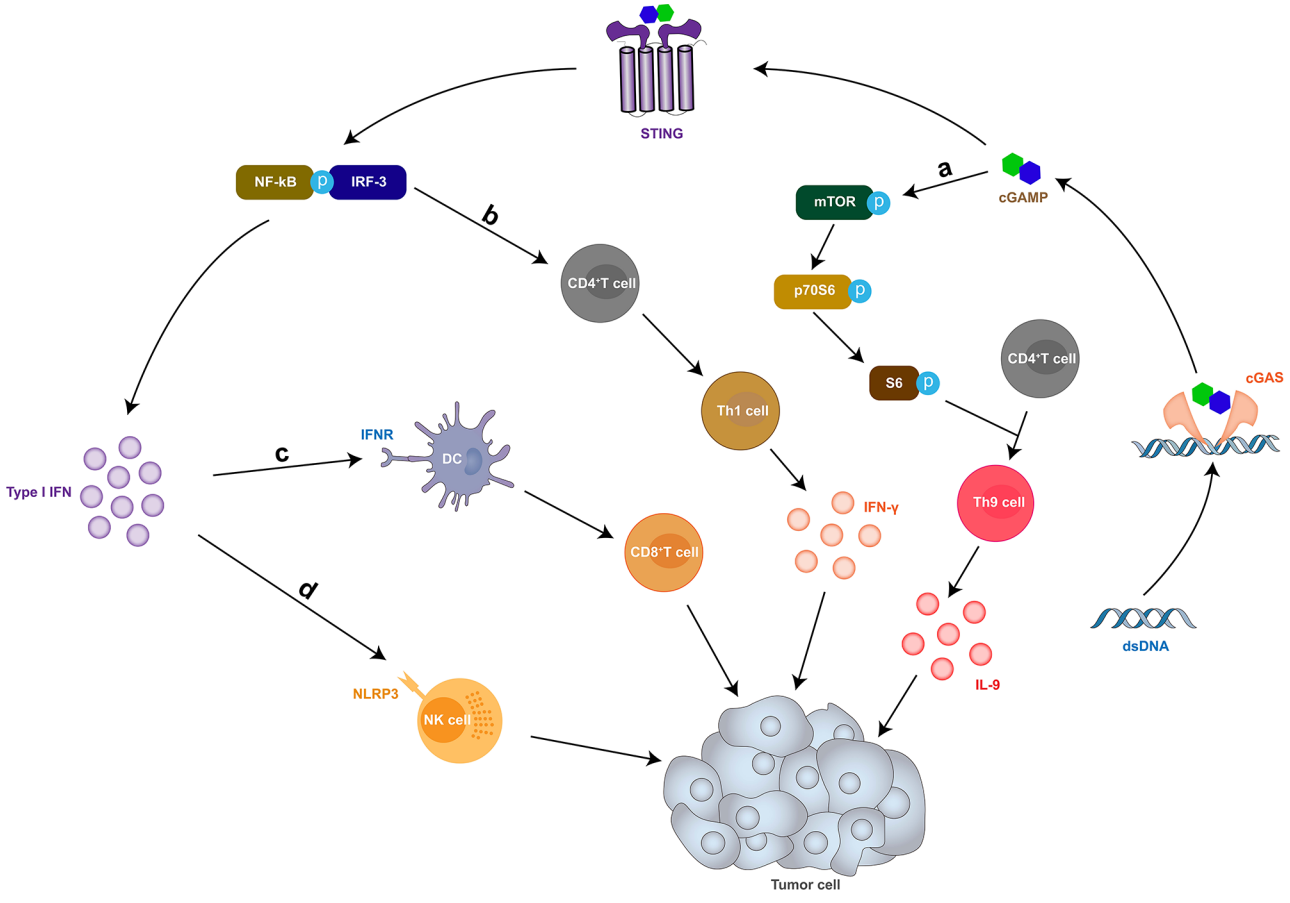

Fig. 2 Regulation of the cGAS-STING pathway in immune cells within the tumor microenvironment. (**a**) STING promotes the differentiation of $CD4^+$ T cells into Th9 cells via GAMP/p70S6K signaling, leading to the secretion of IL-9 and subsequent tumor cell killing; (**b**) STING signaling drives the differentiation of $CD4^+$ T cells into Th1 cells through IRF-3, resulting in the secretion of interferon-γ, which kills tumor cells; (**c**) STING signaling activates dendritic cells (DCs) by inducing the production of type I interferons, further activating $CD8^+$ T cells; (**d**) STING signaling activates natural killer (NK) cells by promoting NLRP3, thereby enhancing tumor cell killing

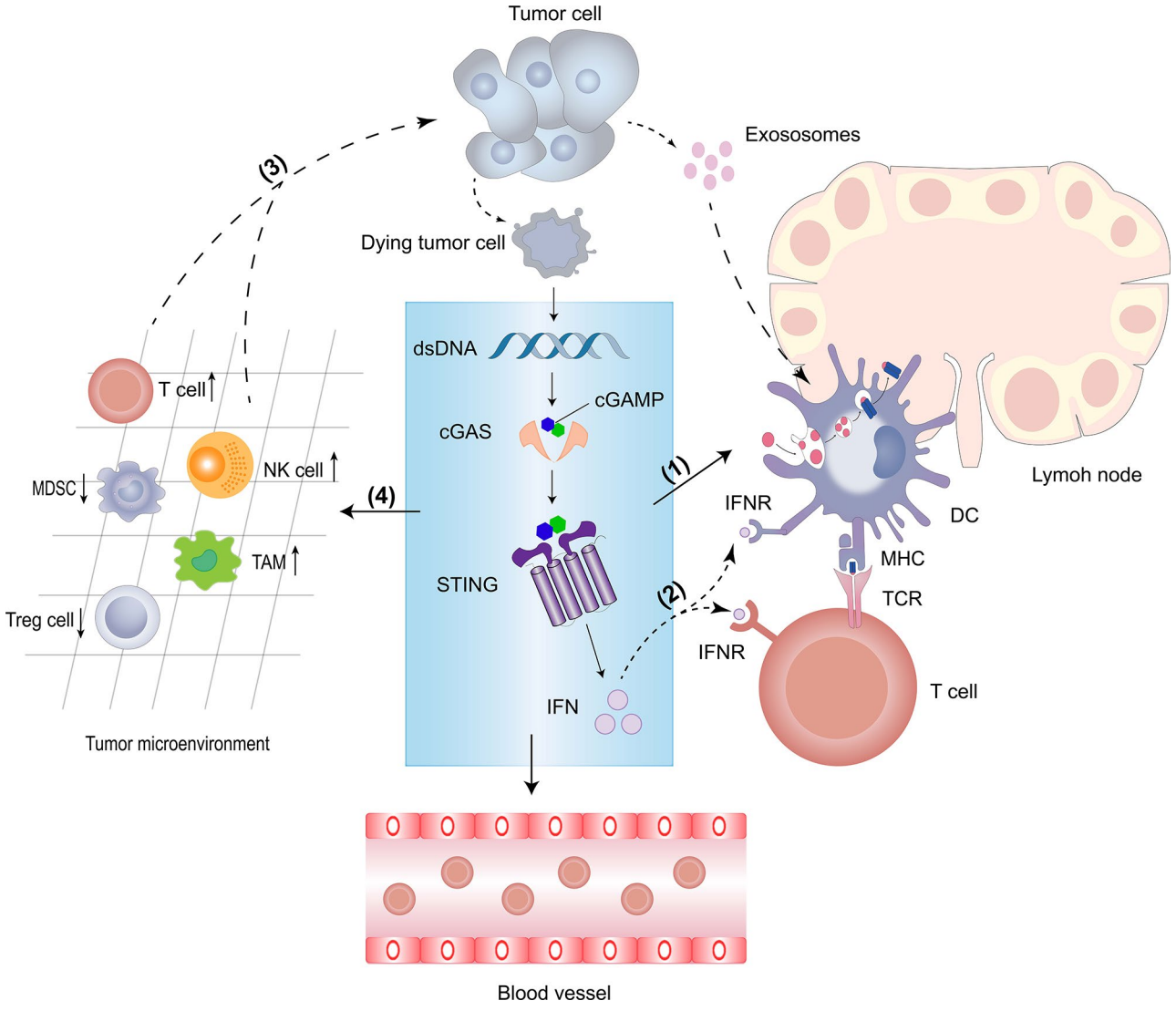

Fig. 3 Role of the cGAS-STING pathway in cancer immunity. The cGAS-STING pathway plays a crucial role in tumor immunity. The key elements are as follows: (1) Enhanced antigen processing and presentation; (2) Promotion of T cell activation and infiltration; (3) Amplification of T cell- and NK cell-mediated tumor eradication; (4) Reprogramming of the immunosuppressive tumor microenvironment

Tumor-derived exosomes have been shown to transfer double-stranded DNA (dsDNA) from cancer cells to dendritic cells (DCs), activating the cGAS–STING pathway and increasing the release of type I interferons (IFNs). These IFNs, in turn, stimulate the expression of costimulatory molecules, including CD40, CD80 and CD86, on DCs, thereby promoting T cell activation. Similarly, irradiated exosomes induce the expression of genes such as IFN-β, Mx1, and IFNAR1 in DCs while also stimulating the secretion of IFN-β, IL-6, and C-X-C Motif Chemokine Ligand 10 (CXCL10), thereby further enhancing the immune response [20–22]. Moreover, receptor-mediated endocytosis targeting specific surface receptors on DCs has emerged as a promising strategy for efficient antigen delivery. Recent studies have demonstrated that the use of CD11c-specific antibodies to target DCs facilitates antigen delivery and promotes DC maturation via the cGAS–STING pathway [23, 24]. Overall, the activation of STING signaling in dendritic cells triggers type I interferon (IFN) secretion and promotes DC maturation. Thus, STING activation in dendritic cells represents a promising approach for cancer immunotherapy.

Promotion of T cell activation and infiltration

T cells are pivotal mediators of the immune response to tumors, with their full effector functions emerging only upon maturation. Within T cells, the STING pathway plays a crucial role in mediating antitumor immunity. Recent studies have highlighted a strong correlation between STING activation and the effector functions of both $CD4^+$ and $CD8^+$ T cells [25, 26]. In $CD4^+$ T cells, STING activation promotes differentiation and

the production of cytokines, including IFN-γ and IL-9 [25]. Specifically, STING-induced activation of IRF-3 and secretion of type I IFNs drive the differentiation of $CD4^+$ T cells into Th1 cells in a cGAMP-dependent manner. Furthermore, cGAMP, a downstream signaling molecule of STING, activates the mTOR pathway, leading to the phosphorylation of downstream effectors such as p70S6 kinase and S6 ribosomal protein. This activation promotes the differentiation of $CD4^+$ T cells into Th9 cells and enhances IL-9 secretion. Both IFN-γ and IL-9 are known to inhibit tumor growth [25]. In $CD8^+$ T cells, STING activation is crucial for maintaining T cell stemness. TCF1 is a transcription factor that plays an essential role in the persistence of $CD8^+$ memory T cells and their capacity to mount secondary immune responses. The expression of TCF1 is upregulated by cGAS-STING pathway-induced IFN signaling; this is critical for the maintenance and functionality of $CD8^+$ T cells [26]. Collectively, these findings suggest that the activation of the cGAS–STING pathway in T cells represents a promising strategy for enhancing the efficacy of cancer immunotherapy. The extravasation of T cells from the vasculature into the tumor microenvironment (TME) is essential for effective tumor eradication by T cells [27]. Activation of the STING pathway in dendritic cells enhances the expression of CXCL9 and CXCL10 in a STING-dependent manner, which is essential for efficient T cell recruitment to the tumor [28–30]. Notably, these chemokines, CXCL9 and CXCL10, also attract NK cells, which enhance antitumor immunity by directly killing tumor cells and facilitating the recruitment of dendritic cells to the tumor. In addition, STING activation in tumor endothelial cells induces the production of type I interferons (IFNs), which in turn stimulate endothelial cells to secrete CXCL10, thereby promoting T cell transmigration across the endothelial barrier [31, 32]. Additionally, STING activation in tumor endothelial cells upregulates key adhesion molecules, including E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), thereby facilitating T cell extravasation [33]. Moreover, intratumoral STING activation not only increases pericyte coverage but also upregulates the expression of adhesion molecules, thereby promoting tumor vascular normalization and enhancing intratumoral T cell infiltration [34, 35]. In conclusion, activation of the STING pathway promotes T cell infiltration into tumors by inducing chemokine expression or normalizing the tumor vasculature.

Amplifying T cell- and NK-cell-mediated tumor eradication

Within the tumor microenvironment, effector T cells engage with MHC-peptide complexes presented on the surface of tumor cells, leading to the destruction of malignant cells. However, in melanoma, the hypermethylation of the cGAS and STING promoters results in their transcriptional silencing, impairing their ability to upregulate the expression of MHC class I molecules and facilitating immune evasion [36]. Encouragingly, the activation of the STING pathway in melanoma cells can restore the expression of MHC class I molecules on tumor cells, thereby improving tumor antigen presentation and enhancing the recognition and elimination of tumor cells by cytotoxic T lymphocytes (CTLs) [36, 37]. Furthermore, STING agonists can enhance the infiltration and activation of cytotoxic T cells within tumors, significantly promoting tumor regression [38, 39]. Throughout tumor progression, a fully functional cGAS–STING signaling axis can inhibit tumor growth by inducing the expression of NKG2D ligands on NK cells, such as RAE1 [40]. In addition, NK cells can target tumor cells with downregulated MHC class I molecule expression, triggering MHC-I-independent antitumor immune responses. Indeed, STING activation within the tumor microenvironment increases the expression of chemokines such as CXCL9, CXCL10, and CCL5, which promote NK cell recruitment [29, 41, 42]. STING activation promotes NOD-like receptor protein 3 (NLRP3) activation to optimize the antitumor function of NK cells [43]. Moreover, STING activation in tumors enhances NK cell activation and cytotoxicity, further facilitating the elimination of tumor cells [44, 45].

Reprogramming the immunosuppressive tumor microenvironment

Immunosuppressive tumor-associated immune cells, including tumor-associated macrophages, myeloid-derived suppressor cells (MDSCs), and regulatory T cells, promote immune escape in the tumor microenvironment by directly or indirectly suppressing T cell-mediated immune responses and fostering an immunosuppressive microenvironment [46]. Consequently, there is a critical need to modulate these immunosuppressive cell populations within the TME to enhance antitumor efficacy. cGAMP, an intermediate signaling molecule in the cGAS-STING pathway, is exchanged across cellular membranes in a cell type-specific manner through several transmembrane channels. Solute carrier (SLC) family members, including SLC19A1 and SLC46A2, mediate the transport of cGAMP into various cell types, such as monocytes and macrophages [47–49]. This regulation of cGAMP uptake and efflux offers an additional layer of control over the intrinsic STING response in cancer cells, ultimately shaping the immune responses within the TME. A study showed that the reduction of extracellular cGAMP significantly reduced populations of $CD11c^+$ (dendritic cells, DC) and $CD103^+$ $CD11c^+$ (conventional type I dendritic cells, cDC1) in the $CD45^+$ MHC II (tumor-associated antigen-presenting cells, APC)

population [50]. In peritoneal colon cancer, tumor cells stimulate the influx of immunosuppressive M2-like macrophages, which subsequently impair the functionality of effector T cells during peritoneal dissemination, thereby fostering an immunosuppressive environment [34]. STING agonists have been shown to inhibit aberrant angiogenesis, enhance pericyte coverage, and normalize the tumor vasculature, thereby promoting the infiltration of activated $CD8^+$ T cells into peritoneal tumor nodules. Moreover, STING activation reprograms tumor-associated macrophages (TAMs) to adopt the M1 phenotype, further enhancing the antitumor immune response [34]. Activation of STING leads to up-regulation of M1-like macrophage-expressed genes as well as down-regulation of M2 macrophage-expressed genes, reprogramming tumor-associated macrophages to the M1 phenotype [34]. Furthermore, STING has been shown to inhibit the expansion and immunosuppressive functions of MDSCs while inducing the secretion of myeloid chemotactic factors by MDSCs. This results in the recruitment of a broad array of immune cells, including monocytes, macrophages, and T cells, to the tumor site [51–53]. STING Inhibits NPC-Derived MDSC induction by enhancing SOCS1 expression in tumor cells and MDSCs [53]. STING activation also reduces the presence of regulatory T cells within the TME, further potentiating antitumor immunity [39, 54]. Furthermore, the cGAS-STING pathway affects other components of the tumor microenvironment. The scientists identified an unintended effect of STING activation on Breg cell expansion, which impairs NK cell-mediated anti-tumor immunity [55]. At the same time, cell-intrinsic cGAS induction promotes the upregulation of CCR5 in $CD8^+$ T cells and induces the production of CCL5 in vascular endothelial cells, thereby promoting the formation of tertiary lymphoid structures (TLS) [56]. STING agonists-activated $mCD11c^+$ DCs also exhibited up-regulated expression of TLS-promoting factors in vitro and in vivo, including lymphotoxin-α (LTA), interleukin (IL)-36, inflammatory chemokines, and type I interferons [57]. These findings underscore the pivotal role of STING signaling in reversing the immunosuppressive functions of tumor-associated immune cells, thereby providing a solid theoretical foundation for the use of STING agonists to reshape the tumor microenvironment and enhance cancer immunotherapy.

Application of the cGAS–STING pathway in cancer therapy

The immunostimulatory potential of the cGAS-STING pathway makes it a compelling pharmacological target in cancer therapy. The activation of this pathway within the tumor microenvironment (TME) effectively induces tumor-specific antigen cross-priming and facilitates effector T cell infiltration. Given its robust anticancer therapeutic potential, the cGAS–STING pathway holds great promise for the development of cancer vaccines, immunotherapies and treatments for virus-associated malignancies (Fig. 4).

Cancer vaccines

Selecting appropriate adjuvants is crucial for overcoming immune tolerance and enhancing tumor-specific immunity. The activation of innate immunity can stimulate antigen-presenting cells (APCs), thereby increasing the immunogenicity of tumor-associated antigens (TAAs) [58]. Therefore, incorporating effective adjuvants is essential for breaking immune tolerance and enhancing tumor-specific immune responses. Evidence suggests that the activation of the innate immune system not only enhances pre-existing TAA specificity but also induces robust tumor-specific immunity [58]. Various adjuvants, such as attenuated tuberculosis vaccines, have been widely used in the development of cancer vaccines [59]. The codelivery of adjuvants and TAAs typically induces a Th1-skewed immune response [58]. The adjuvant activity of cyclic dinucleotides (CDNs) has been confirmed in the development of H5 influenza vaccines [60]. Given the pivotal role of STING in initiating innate immune responses, STING agonists have been proposed as potential adjuvants for cancer vaccines [61]. Fu et al. were the first to evaluate the efficacy of STINGVAX, a cancer vaccine based on a STING agonists, in various tumor-bearing mouse models. Composed of CDNs- and GM-CSF-secreting cancer cells, STINGVAX significantly inhibited tumor growth in B16 melanoma-bearing mice, showing a dose-dependent therapeutic effect [62]. Notably, the infiltration of $CD8^+$ IFN-γ^+ T cells and DCs into tumor tissues were markedly greater in STINGVAX-treated mice than in those receiving GM-CSF-secreting cancer cell vaccines without CDNs [62]. The efficacy of STINGVAX was also demonstrated in models of colon cancer, gastrointestinal squamous cell carcinoma, and pancreatic cancer [62]. Further investigations revealed that synthetic CDNs exert potent immunostimulatory effects on both mouse and human dendritic cells [62]. The feasibility of STING-based vaccines was subsequently confirmed in melanoma and pancreatic cancer models [63, 64]. Additionally, Miao et al. developed a cyclic lipid nanoparticle (LNP) formulation that served as an effective STING agonists for antigen-specific mRNA vaccine delivery [65]. Subcutaneous injection of LNP increased infiltration of macrophages; dendritic cells and natural killer cells (NK cells) while inducing significant antigen-specific cytotoxic T-lymphocyte (CTL) responses, creating a robust immune response [65]. This lipid nanoparticle (LNP) formulation, containing lipids with cyclic amine head groups, activated the STING pathway and significantly prolonged survival in mouse

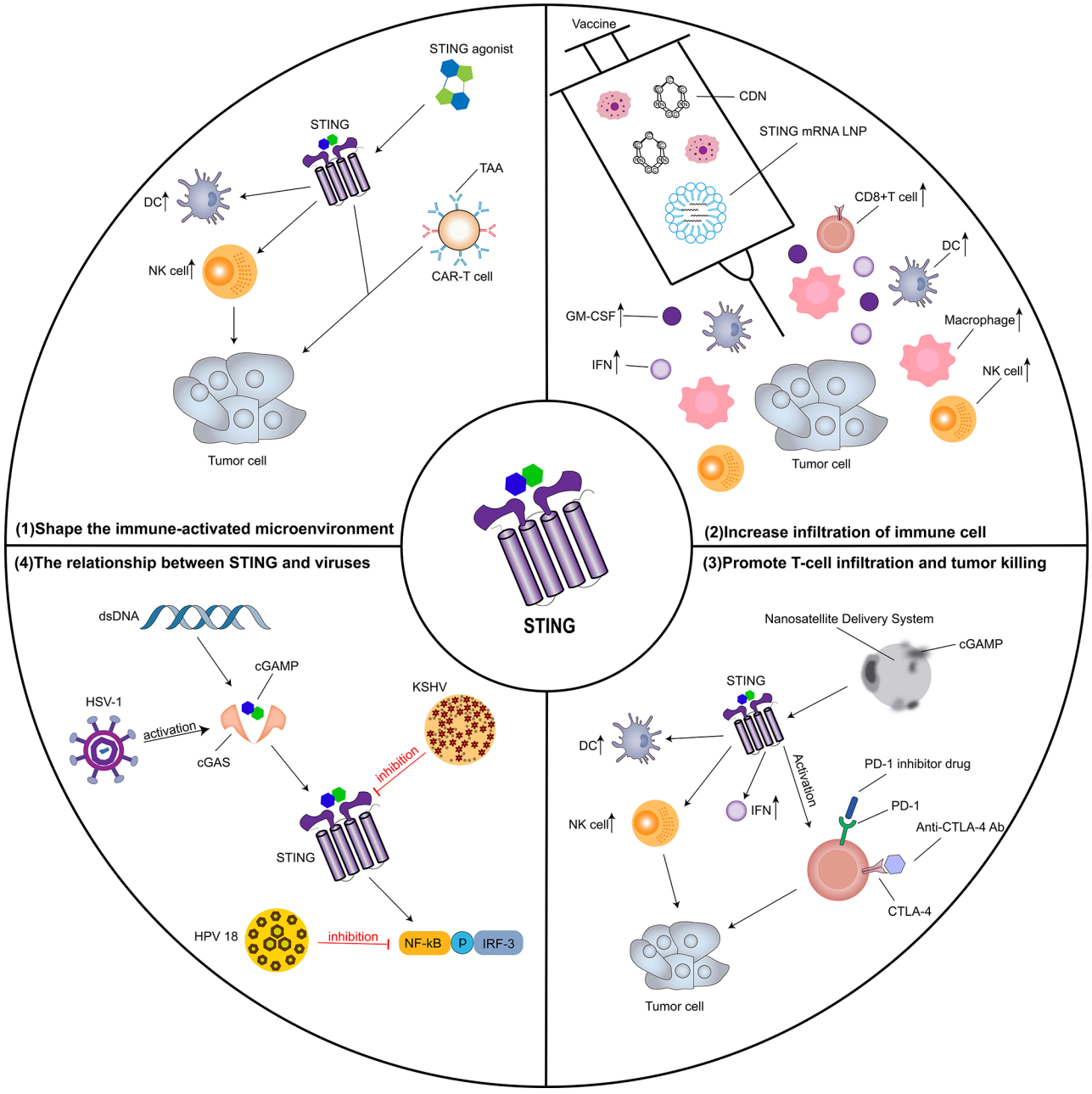

Fig. 4 The application of the cGAS–STING pathway in cancer therapy (1). STING agonists activate STING, leading to the recruitment and activation of immune-related cells, such as dendritic cells (DCs) and natural killer (NK) cells. In turn, these immune cells shape a tumor microenvironment that enhances the efficacy of CAR-T cell therapy; (2) Injection of a STING-based tumor vaccine into tumor tissues increases the infiltration of DCs, CD8 + T cells, and NK cells, as well as stimulates the secretion of IFN, thereby inducing a robust immune response; (3) A nanosatellite delivery system carrying the STING agonist cGAMP activates STING, leading to the recruitment of immune-related cells and the promotion of T cell activation. This enhances the efficacy of anti-PD-1 and anti-CTLA-4 antibodies in tumor elimination.; (4) The cGAS-STING pathway is closely linked to viral infections. Herpes simplex virus type 1 (HSV-1) activates the cGAS-STING pathway, whereas other viruses, including human papillomavirus type 18 (HPV18) and Kaposi's sarcoma-associated herpesvirus (KSHV), suppress its activation

models, highlighting the therapeutic potential of STING agonists in cancer treatment [65].

Immune checkpoints

Programmed cell death protein 1 (PD-1) is a critical immune checkpoint receptor expressed on activated T cells that functions as a key immune suppressor. PD-L1, the ligand of PD-1, is implicated in immune suppression and transmits inhibitory signals that prevent T cell activation. Tumor cells can upregulate PD-L1 expression, and when they bind to PD-1, this interaction provides a negative regulatory signal to T cells, effectively inhibiting

their ability to recognize and attack cancer cells—a mechanism that facilitates immune evasion by tumors. Anti-PD-1/PD-L1 therapies aim to block this immunosuppressive signal, thereby enhancing T cell functionality. STING agonists activate the STING pathway, promoting T cell activation and function, which in turn augments the therapeutic efficacy of anti-PD-1/PD-L1 treatments. Thus, STING agonists serve as ideal sensitizers, amplifying the effects of anti-PD-1/PD-L1 therapies by enhancing T cell activation and tumor infiltration. The presence of pre-existing mature cytotoxic T lymphocytes (CTLs) is a critical prerequisite for optimal therapeutic outcomes in patients receiving anti-PD-1/PD-L1 treatments. Anti-PD-1/PD-L1 therapies can counteract the immunosuppressive effects of cGAS-STING agonists [66]. Tan et al. developed the SatVax vaccine using cGAMP and antigenic peptides (Q19D, Q15L), which, when combined with anti-PD-L1 therapy, significantly enhanced E7-specific $CD8^+$ CTLs and reduced the proportion of $CD8^+$ $Tim3^+$ and $CD8^+$ $PD\text{-}1^+$ T cells [67]. This combination therapy resulted in marked tumor regression, with 4 out of 5 mice achieving a complete tumor-free status [67]. Like the nanomolecular satellites in SatVax, poly (β-amino ester) (PBAE) nanoparticles can also increase CDNs delivery [68]. Compared with anti-PD-1 or CDNs-free treatments, PBAE-CDNs combined with an anti-PD-1 antibody significantly delayed tumor growth in B16 melanoma model mice [68] Notably, in various xenograft models, mice that received STING agonists in combination with anti-PD-1 treatment were resistant to tumor rechallenge [62, 69]. It has been shown that while anti-PD-1 monotherapy failed to induce antitumor effects in a B16-F10 mouse melanoma lung metastasis model, the combination of STING-LNP and anti-PD-1 exhibited synergistic antitumor effects. The study demonstrated that STING-LNP treatment significantly upregulated the expression of CD3, CD4, NK1.1, PD-1, and interferon (IFN)-γ in lung metastases. This effect was mediated by type I IFN production in liver macrophages that had internalized STING-LNP, which, in turn, triggered systemic activation of $PD\text{-}1^+$ NK cells. The IFN-γ produced by these activated NK cells induced PD-L1 expression in cancer cells, leading to a synergistic antitumor effect when combined with anti-PD-1 therapy [70]. These findings suggest that combining STING agonists with anti-PD-1/PD-L1 agents can increase anticancer efficacy.

Anti-CTLA-4 therapy lowers the activation threshold of T cells, thereby amplifying tumor-specific immune responses [71]. Shane et al. demonstrated that an intact cGAS–STING pathway is essential for maximizing the efficacy of anti-CTLA-4 therapy [72]. Using a B16 syngeneic melanoma mouse model and in vitro radiotherapy, they showed that mice receiving radiation and tumor cell injections followed by anti-CTLA-4 therapy exhibited increased tumor elimination. In contrast, mice with STING-deficient tumors showed a reduced therapeutic response [72]. Additionally, STING deficiency significantly impaired $CD8^+$ T cell infiltration into the tumor microenvironment. Ager et al. explored the effect of combining anti-CTLA-4, anti-PD-1, and anti-4-1-BB antibodies in prostate cancer models [73]. This combination resulted in the regression of bilateral tumors in 40% of the mice, whereas the addition of the STING agonists CDG and triple checkpoint blockade led to complete regression in 75% of the mice [73]. Further analysis revealed that the local delivery of CDG and ICIs increased SPAS-specific $CD8^+$ T cells within tumors and that the proportion of these cells within the tumor-infiltrating $CD8^+$ T cell population was significantly elevated. Consequently, CDG combined with ICIs effectively expanded the TCR repertoire and activated immune responses against subdominant antigens [73].

Viral interactions

As previously highlighted, the integrity of the cGAS-STING pathway is crucial for the host's defense against DNA viruses, retroviruses, and intracellular bacterial pathogens [74–76]. Disruptions or deficiencies in this pathway have been identified in various cancers, including colon cancer and melanoma [77]. For cancer patients with impaired cGAS–STING signaling, oncolytic virotherapy is a promising therapeutic strategy [78]. Xia et al. demonstrated the effectiveness of this approach by using herpes simplex virus type 1 (HSV-1) with a γ-34.5 gene deletion to establish a melanoma mouse model [78]. The γ34.5 protein, which normally suppresses the host's innate immune response, is absent in HSV-1Δγ34.5. This absence results in the activation of the cGAS–STING pathway, leading to increased viral clearance in normal cells [78]. However, in tumors deficient in cGAS-STING signaling, the lack of an antiviral response leads to uncontrolled viral replication and eventual cell death. Notably, melanoma cells lacking STING are more susceptible to HSV-1Δγ34.5 infection [78]. Additionally, Barber et al. reported that cGAS-STING-deficient mice exhibited a significantly enhanced response to intratumor injections of HSV-1Δγ34.5 in an ovarian cancer model [79]. Given the frequent inactivation of the cGAS–STING pathway across a range of cancers, oncolytic virotherapy appears to be a rational treatment strategy for certain cancer subsets. Moreover, some oncogenic viruses are known to selectively inhibit the activation of NF-κB or IRF-3 downstream of STING, thereby evading the host's innate immune surveillance. Lau et al. were the first to identify oncogenic viral proteins, such as HPV18 E7 and adenovirus E1A, as potent inhibitors of the cGAS-STING pathway. Both E1A and E7 bind directly to STING, and silencing these oncogenes in human tumor cells restores

cGAS–STING signaling, suggesting the potential role of host–virus interactions in the evolution of viral oncogenes [80]. Kaposi's sarcoma-associated herpesvirus (KSHV) ORF52, an abundant γ-herpesvirus protein, has been shown to inhibit cGAS activity by interfering with cGAS–DNA binding, thus disrupting the cytoplasmic DNA-sensing process [81]. HPV18 E7 selectively antagonizes STING-mediated NF-κB activation but does not affect IRF-3 activation. HPV18 E7 binds to a critical region of the NF-κB signaling cascade and prevents the nuclear accumulation of p65. Furthermore, the inhibition of STING-induced NF-κB activation by E7 is linked to HPV pathogenicity and contributes to an increased likelihood of tumorigenesis [82].

CAR-T cells

By transferring the gene encoding CAR, engineered T cells can specifically recognize target antigens on tumor cells through single-chain variable fragment (SCFV) structural domains [83]. CAR-modified T cells do not rely on MHC activation and directly kill tumor cells [84]. CAR-T cell therapy has been successfully applied to hematologic diseases, but its effectiveness in solid tumors remains limited [85]. It is widely accepted that an immunosuppressive tumor microenvironment and intratumor heterogeneity are the primary factors driving immune evasion by CAR-T cells [86]. Smith et al. designed a novel implantable bioactive carrier that delivers CAR-T cells to the tumor surface [87]. Compared with the systemic delivery of CAR-T cells, the delivery of this bioactive vector significantly enhances T cell expansion and tumor control. CAR-T cell therapy significantly prolonged survival time, but this intervention did not completely eliminate tumors in mice [87]. Under selection pressure, tumor cells with high expression of the target (RAE1) were destroyed, whereas RAE1^low/negative tumor cells survived. As a result, all the mice became resistant to CAR-T cell therapy [87]. Bioactive scaffolds have been modified with the STING agonists cyclic di-GMP (cdGMP). The codelivery of generated cdGMP and CAR-T cells significantly increased the activation of TCR/CD3 signaling and downstream pathways in circulating tumor-specific T cells [87]. In a mouse pancreatic tumor model, the codelivery of CAR-T cells and cdGMP completely cleared tumors and significantly prolonged survival in 4 of 10 mice [87]. To further investigate the systemic antitumor immunity induced by this combination therapy, four fully regressed mice were rechallenged with intravenous injections of tumor cells. Notably, prior combination therapy inhibited the formation of detectable tumor masses [87]. In a recent study, the researchers screened a novel anti-CD70 scFv and generated CD70 CAR-T cells, which exhibited potent anti-tumor function against CD70 renal cancer cells (RCC) both in vitro and in vivo. The article demonstrates that PARPi modulates the tumor microenvironment (TME) by activating the cGAS-STING pathway, altering the balance of immunostimulatory signaling and enabling low-dose CAR-T cell therapy to induce effective tumor regression [88]. Meanwhile, a newly developed STING agonists, IMSA101, stimulates IL-18 secretion and enhances the efficacy of CAR-T cell therapy [89]. We propose that STING agonists can increase the efficacy of CAR-T cell-induced in situ cancer vaccines and elicit a durable systemic antitumor immune response.

Development of STING agonists and recent advances in the STING pathway

Following the discovery of the cGAS-STING signaling pathway, targeting its activation has emerged as a promising strategy for cancer therapy. As the key mediator in the cGAS-STING pathway, STING plays a pivotal role in initiating immune responses that drive tumor eradication. Over the years, several types of STING agonists have been developed and can be categorized into natural cyclic dinucleotide (CDN) agonists, synthetic CDN agonists, and small-molecule STING agonists, all of which have been shown to be highly effective in antitumor therapy (Table 1).

Natural CDN STING agonists

As the molecular mechanisms of the cGAS-STING signaling pathway have become increasingly understood, the development of STING agonists has focused primarily on cyclic dinucleotides (CDNs), which naturally serve as STING ligands; these include bacterial-derived secondary signaling molecules such as c-diGMP, c-diAMP, and 3′,3′-cGAMP, each containing two uniform 3′-5′ phosphodiester linkages. Additionally, the endogenous 2′,3′-cGAMP, synthesized by cGAS, features a hybrid 2′-5′ and 3′-5′ bond structure [90, 91]. In vitro studies have demonstrated that c-diGMP inhibits the proliferation of human colon cancer cells [92] and acts as an adjuvant to significantly increase the antitumor efficacy of therapeutic vaccines in tumor-bearing mouse models [64, 93]. Similarly, c-diAMP induces apoptosis in estrogen receptor-negative breast cancer cells through a STING-dependent mechanism [94]. Moreover, c-diAMP elicits a potent T cell response in mice immunized with soluble antigens or targeted dendritic cells (DCs) [95]. Furthermore, engineering Bacillus Calmette–Guerin (BCG) to overexpress c-diAMP promotes macrophage polarization toward an inflammatory phenotype, enhances T cell activation, and decreases Treg cell numbers, thereby achieving superior antitumor efficacy in urothelial carcinoma mouse models compared with wild-type BCG [96]. Likewise, 3′,3′-cGAMP induces apoptosis in malignant B cells, promotes tumor regression, and extends survival

Table 1 Overview of STING agonists in Cancer therapy

Types	Drug Names	Dosing route	Indications	mouse strains	Development stage	Results	References
Natural STING agonists	c-diGMP	Intravenous injection	Melanoma	C57BL/6	Pre-clinical	Generated large numbers of antigen-specific CD8 T cells capable of recognizing tumor cells and produced significant therapeutic anti-tumor effects in mice	[64]
	c-diAMP	Intratumoral injection	Bladder	C57BL/6	Pre-clinical	Significant reduction in tumor volume and a significant reduction in tumor weight.	[96]
	3′,3′-cGAMP	Intraperitoneal infection	B-cell malignant tumor	NSG	Pre-clinical	Significantly inhibited tumor growth in a mouse myeloma model. Moreover, the migration of myeloma cells was inhibited to some extent.	[97]
	2′,3′-cGAMP	Intravenous infection	Adenocarcinoma of the colon	BALB/c	Pre-clinical	significant reduction in tumor volume, a significant reduction in tumor weight, and a significant increase in survival rate in mice.	[98]
Synthetic STING agonists	ADU-S100	Intratumoral injection	Advanced solid tumors; lymphomas;	-	Phase 1	Developed a good therapeutic effect in patients with fewer adverse effects	[101]
	MK-1454	Intratumoral injection	Advanced solid tumors; lymphomas; head and neck cancer	-	Phase 1	The efficacy of MK-1454 in combination with Pembrolizumab was encouraging, with regression of both injectable and non-injectable lesions	[104]
	E7766	Intratumoral injection	Triple-negative breast cancer	BALB/c	Pre-clinical	Significantly enhances the efficacy of eribulin, promoting IFN release as well as the immune response in vivo. Tumor growth was significantly inhibited and survival rate was significantly improved in bladder tumor.	[106]
Small molecule STING agonists	diABZI	Intravenous injection	Colon tumor	BALB/c	Pre-clinical	Tumor growth was significantly inhibited and survival was significantly improved.	[110]
	Triazole 40	Intravenous injection	Breast cancer	BALB/c	Pre-clinical	Resulted in significant inhibition of tumor growth and increased survival rate	[111]
	4c	Intravenous injection	Colorectal cancer	BALB/c	Pre-clinical	Significant inhibition of tumor growth and improved survival	[112]
	24b	intravenous injection	Colorectal cancer	BALB/c	Pre-clinical	Significant inhibition of tumor growth and increased survival rate	[113]
	MSA-2	Oral	Melanoma; colorectal cancer	C57BL/6	Pre-clinical	Tumor growth was significantly inhibited and survival rate was significantly increased	[114]
	SR-717	Intraperitoneal injection	Melanoma	C57BL/6	Pre-clinical	Significant inhibition of tumor growth and improved survival rate	[115]
	MK2118	Intratumoral injection	advanced solid tumors; lymphomas	-	Phase 1	Showing a more pronounced immune response	[116]

in mice with B-cell malignancies [97]. Additionally, 2′,3′-cGAMP has been shown to upregulate the expression of antitumor cytokines, such as IFN-β and IFN-γ, stimulate dendritic cell (DC) activation, and induce tumor cell apoptosis, resulting in significant antitumor activity in tumor-bearing mice [98]. In summary, natural cyclic dinucleotides (CDNs) show significant promise as adjuvants for therapeutic vaccines and as immunotherapeutic agents in preclinical studies.

Synthetic CDN STING agonists

Given the limitations of natural CDNs in cancer therapy, considerable efforts have been made to develop CDN-based STING agonists, incorporating modifications aimed at enhancing their stability and therapeutic efficacy. To increase enzymatic stability, sulfur atoms have been introduced to replace the nonbridging oxygen atoms in the phosphodiester bond, resulting in thiophosphate analogs [99]. Among these, ADU-S100 (also known as MIW815) has been shown to resist degradation by phosphodiesterases and bind more effectively to both murine and human STING than unmodified CDNs [99]. The intratumoral injection of ADU-S100 triggers a robust $CD8^+$ T cell response and promotes the regression of esophageal adenocarcinoma [100]. Recently, ADU-S100 has entered clinical trials because of its promising

antitumor activity. In a phase I study involving patients with advanced or metastatic cancers, ADU-S100 was well tolerated and stimulated systemic immune activation. However, its clinical activity as a monotherapy is limited (NCT02675439) [101, 102]. Therefore, further investigation is needed to identify the factors contributing to the disappointing clinical outcomes of ADU-S100. In addition to ADU-S100, other modified CDN-based STING agonists have been developed. MK-1454, a novel CDN developed by Merck, has a high affinity for STING in vitro and strongly induces IFN-β secretion [103]. Moreover, the intratumoral injection of MK-1454 induces complete tumor regression and enhances the antitumor effects of anti-PD-1 therapy in syngeneic tumor-bearing mice [103]. These promising results have led to ongoing clinical trials evaluating the safety and efficacy of MK-1454, either alone or in combination with pembrolizumab, for the treatment of advanced solid tumors or lymphomas (NCT03010176). Preliminary data suggest that although MK-1454 has limited efficacy as a monotherapy, its combination with pembrolizumab has shown encouraging results, including tumor regression in both injectable and noninjectable lesions [104]. As CDNs adopt a U-shaped conformation when binding to the STING dimer, the introduction of a cross-ring macrocycle to link nucleic acid bases has led to the development of large-ring STING agonists, such as E7766 [105]. E7766 has an increased ability to activate innate immune pathways, supporting its use in combination with immunotherapies for the more effective treatment of triple-negative breast cancer (TNBC) and other malignancies [106]. Furthermore, the intravesical injection of E7766 in a high-risk nonmuscle invasive bladder cancer (NMIBC) animal model has shown promising results, including the induction of immune memory in treated animals [107]. In conclusion, compared with natural CDNs, synthetic CDN-based STING agonists exhibit superior enzymatic stability and antitumor activity. These preclinical findings have led to the initiation of clinical trials evaluating CDN-based synthetic STING agonists, either alone or in combination with immune checkpoint inhibitors, for the treatment of advanced solid tumors and lymphomas.

Small-molecule STING agonists

Compared with CDN-based STING agonists, small-molecule STING agonists offer several distinct advantages: [1] improved drug likeness [2], enhanced pharmacokinetics [3], superior access to cytoplasmic targets [4], straightforward chemical synthesis, and [5] greater structural diversity [108, 109]. Consequently, the development of STING agonists has increasingly focused on non-CDN-derived small molecules, which have the potential for systemic administration and the ability to target multiple tumor sites throughout the body. Recent high-throughput screening by scientists at GlaxoSmithKline identified a series of aminobenzimidazole (ABZI)-based compounds as moderate STING agonists. Crystallographic analyses revealed that ABZIs bind to the STING dimer at a 2:1 ratio, with side chains tightly packed to minimize unfavorable interactions with the protein. On the basis of these findings, the researchers covalently linked two ABZI molecules using a four-carbon chain, optimizing the compound to yield bis-benzimidazole (diABZI). diABZI demonstrated 400-fold greater potency than cGAMP in activating STING in human peripheral blood mononuclear cells (PBMCs) and similarly induced robust STING activation in murine PBMCs. When administered intravenously, diABZI significantly inhibited tumor growth in colorectal tumor-bearing mice and improved survival, with 80% of treated mice remaining tumor free after the study [110]. This discovery prompted the development of several aminobenzimidazole derivatives as STING agonists. For example, triazole 40, derived from diABZI, is a potent activator of both human and murine STING, exhibiting improved solubility and pharmacokinetic properties. The intravenous administration of triazole 40 in established 4T1 breast cancer-bearing mice significantly inhibited tumor growth while demonstrating good safety and tolerability [111]. Similarly, compound 4c, optimized from diABZI through chemical substitution, effectively stimulates STING signaling and induces IFN-β secretion in PBMCs. The intravenous administration of 4c significantly reduced tumor growth in CT26 colorectal tumor-bearing mice. Notably, 4c treatment also induced antitumor immune memory, preventing tumor relapse [112]. Additionally, compared with 2′,3′-cGAMP, compound 24b was found to induce higher levels of IFN-β, CXCL10, and IL-6 in PBMCs. When administered at 0.15 mg/kg in intermittent intravenous doses, 24b significantly inhibited tumor growth in CT26 tumor-bearing mice [113].

A recent study by Merck introduced MSA-2, an oral benzothiophene-based STING agonists that activates TBK1 and IRF-3 phosphorylation, inducing IFN-β secretion in human THP-1 monocytes in a STING-dependent manner [114]. Owing to its low pKa, MSA-2 demonstrates superior cellular permeability and efficacy in the acidic tumor microenvironment, making it a selective tumor-targeting agent suitable for systemic administration. MSA-2 has also demonstrated dose-dependent antitumor activity in MC38 syngeneic tumor models, resulting in complete tumor regression in 80–100% of treated mice [114]. Notably, 95% of these tumor-free mice were resistant to tumor rechallenge, suggesting that MSA-2 induces immune memory in treated animals [114]. Furthermore, MSA-2, in combination with anti-PD-1 antibodies, has synergistic antitumor effects and extends the overall survival of tumor-bearing mice [114].

A recently developed small-molecule STING agonists, SR-717, was identified through high-throughput screening and chemical modification [115]. SR-717 binds to both human and murine STING, with crystallographic analysis showing that two SR-717 molecules occupy the cleft of the STING dimer, activating STING in a manner analogous to that of 2′,3′-cGAMP. In B16 melanoma-bearing mice, SR-717 effectively suppressed tumor growth and extended survival in a STING-dependent manner, with daily intraperitoneal administration for up to 7 days. Furthermore, SR-717 inhibited B16 lung metastasis formation [115]. In contrast to MSA-2, no therapeutic benefit was observed when SR-717 was combined with anti-PD-1/PD-L1 antibodies in B16 tumor-bearing mice, potentially due to differences in their molecular characteristics [115]. A recent clinical trial demonstrated that MK-2118 (a non-cyclic dinucleotide STING agonist) can induced systemic immune effects in patients who received intra-tumoral injections [116]. These novel STING agonists have shown promise for human clinical application, with systemic administration in syngeneic tumor models resulting in sustained tumor regression and synergistic effects with immune checkpoint inhibitors. However, these agents remain in preclinical or early clinical stages, and substantial challenges must be overcome before their clinical adoption in cancer therapy.

Other agents

In addition to STING agonists, several other agents can also activate STING indirectly and may provide enhanced cancer inhibition. Ataxia telangiectasia mutated (ATM) is a key regulator of the DNA repair system. It was demonstrated that inhibition of ATM activated the cGAS-STING pathway and increased MHC class I expression in colorectal cancer (CRC) cells, leading to significant tumor suppression [117]. PARP inhibitors are potent agents used in breast cancer treatment that may enhance the efficacy of radiotherapy and chemotherapy with alkylating and platinum agents by inhibiting DNA damage repair and promoting apoptosis in tumor cells. However, these inhibitors have shown limited effectiveness in patients with advanced BRCA-mutated breast cancer. Notably, systemic administration of STING agonists overcomes the multilayered suppression of tumor cell-mediated immune responses and synergistically inhibits tumor growth when combined with PARP inhibitors in a mouse model of BRCA1 deletion-driven mammary tumors [118]. Furthermore, a recent study proposes that sacituzumab, a type of tropomyosin-related receptor kinase (TRK) inhibitor, inhibits topoisomerase I, leading to STING activation and enhanced antitumor immunity [119]. It has been proposed that manganese, through activation of the cGAS-STING pathway, is essential for host defense against DNA viruses [120]. Manganese enhances adaptive immune responses through activation of the cGAS-STING pathway and synergistically improves efficacy in a mouse model of melanoma when combined with immune checkpoint inhibition [121]. ENPP1 (ectonucleotide pyrophosphatase phosphodiesterase 1) is an enzyme that hydrolyzes cGAMP, thereby inhibiting STING activation. Blockade of ENPP1 represents a unique strategy for triggering immune remodeling and harnessing the STING pathway [122]. Furthermore, inactivation of cell cycle-related proteins also leads to the activation of STING signaling. TTK is an essential component of the spindle assem bly checkpoint (SAC), TTK inhibitor OSU13 display DNA damage and micronuclei that trigger the cytosolic DNA-sensing cGAS-STING pathway [123]. A study identified that small molecule inhibitor targeting TTK (CFI-402257) induced cytosolic DNA, thereby activated DDX41-STING cytosolic DNA sensing pathway to produce senescence-associated secretory phenotypes (SASPs) in HCC cells. These SASPs subsequently led to recruitment of different subsets of immune cells (natural killer cells, $CD4^+$ T cells, and $CD8^+$ T cells) for tumor clearance [124].

Challenges of the cGAS-STING pathway in cancer therapy

As previously discussed, the activation of the cGAS-STING signaling pathway can enhance the tumor immune microenvironment and effectively inhibit tumor progression. However, there are also unfavorable factors associated with STING in the tumor microenvironment. ENPP1 (ectonucleotide pyrophosphatase phosphodiesterase 1), an enzyme that degrades cGAMP, is often highly expressed on the surface of cancer cells. It breaks down cGAMP when released from within the cell into the extracellular space, thereby inhibiting the cGAS-STING pathway and facilitating immune escape [125]. Furthermore, under certain conditions, the activation of cGAS-STING has been shown to facilitate tumor progression. For example, in the F10 mouse melanoma model, treatment with the STING agonists SR-717 induces the anticipated antitumor immune response, inhibiting tumor growth; however, it also upregulates the expression of PD-L1 and IDO, thereby promoting immune evasion [115]. Ionizing radiation activates the STING-TANK-binding kinase 1 (TBK1)-interferon regulatory factor 3 (IRF-3) innate immune pathway, leading to the upregulation of PD-L1 expression in hepatocellular carcinoma (HCC) cells, the inhibition of cytotoxic T lymphocyte activity and the protection of tumor cells from immune-mediated destruction [126].

In senescent and chromosomally unstable tumor cells, DNA damage-induced leakage of DNA activates the cGAS-STING pathway. External events such as telomere shortening, radiation, chemotherapy, and elevated

reactive oxygen species (ROS) levels can cause DNA damage, leading to the accumulation of DNA fragments in the cytoplasm that activate the cGAS-STING signaling cascade. Telomeres, which typically protect chromosomal ends during cell division, prevent DNA ends from being recognized as double-strand breaks (DSBs), thus preventing the induction of the DNA damage response (DDR). However, when telomeres shorten beyond a certain threshold, DNA ends become exposed and are recognized as DSBs, activating the cGAS–STING pathway and triggering a senescence-associated secretory phenotype (SASP) [127]. The SASP, which is rich in inflammatory cytokines, fosters an inflammatory microenvironment. While acute inflammation is often considered to have anticancer effects, chronic inflammation contributes to tumorigenesis, promotes drug resistance and increases metastasis [128]. In a lung adenocarcinoma metastasis model, systemic treatment of mice with STING agonists eliminates dormant metastases and prevents spontaneous outbreaks in a T-cell and natural killer cell-dependent manner [129]. A report has shown that activation of STING affects calcium homeostasis in T cells, leading to endoplasmic reticulum stress and subsequent T cell death [130]. In addition to telomere shortening, defects in homologous recombination, spindle assembly checkpoint abnormalities, and oncogene overexpression also contribute to genomic instability and micronucleus formation [131]. DNA fragments released from micronuclei in the cytoplasm activate the downstream cGAS–STING pathway, with STING-activated NF-κB signaling potentially contributing to tumor progression [132]. In a mouse breast cancer model, cGAMP generated by cytoplasmic dsDNA release was found to be transferred from tumor cells to astrocytes via gap junctions, activating STING in astrocytes and inducing the paracrine production of IFN-α and TNF, which in turn activated STAT1 and NF-κB in tumor cells, facilitating brain metastasis [133]. Non-canonical activation of the cGAS-STING pathway produces IL-6. STING-mediated NF-κB activation induces the expression of IL-6 in triple-negative breast cancer cells and activates pSTAT3, thereby enhancing cell survival and PD-L1 expression. Combination treatment with STING agonists, doxorubicin, and STAT3 inhibitors can inhibit cell survival and clonogenicity in triple-negative breast cancer cell [134]. The study demonstrated that half of the STING-expressing cancer cells rapidly increase pro-tumor IL-6 expression following genotoxic DNA damage, typically independent of the type I IFN response. As a result, pharmacological inhibition of STING does not broadly suppress CPT-induced IL-6 production. However, the authors showed that inhibition of ERK1/2 can suppress the pro-tumor response to DNA damage while preserving the anti-proliferative effects of the STING-interferon axis [135]. Recent studies have shown that in triple-negative breast cancer, chromosomal instability (CIN) leads to the activation of cGAS-STING signaling, with cGAS-STING-dependent IL-6 production upregulated following CIN. As an upstream activator of STAT3, cGAS-STING-induced IL-6 and atypical NF-κB production promote the survival of triple-negative breast cancer tumor cells. Combination treatment with cGAS-STING agonists and tocilizumab may reduce the adverse effects of IL-6, leading to improved therapeutic outcomes [136]. Beyond triple-negative breast cancer, the cGAS-STING axis exhibits diverse roles across various cancer types. Head and neck squamous cell carcinoma (HNSCC) undergoing necroptosis releases distinct damage-associated molecular patterns (DAMPs), which, in turn, activate the cGAS-ISG15-RAGE axis to promote tumor cell invasion and lymphatic metastasis [137]. In malignant B-cell tumors, STING agonists can directly eliminate malignant B cells. However, STING activation also triggers the IRE1/XBP1 pathway, which partially protects agonist-stimulated malignant B cells from apoptosis [97]. In bladder cancer, STING activation induces the production of type I interferons, which, in turn, enhance the stemness of bladder cancer (BC) cells via the WNT5A paracrine pathway, promoting the formation of cancer-associated fibroblasts (CAFs). Patients with a high proportion of intratumoral SLC14A1-expressing CAFs exhibit poor prognosis and reduced response rates to chemotherapy and immunotherapy [138]. Mitochondrial dysfunction also triggers mtDNA leakage, activating the cGAS–STING pathway and promoting tumor progression through immune checkpoint regulation while fostering an inflammatory tumor microenvironment [139]. Recent studies have shown that STING agonists induce B cells to express IL-35, which in turn suppresses NK cell proliferation and impairs NK cell-mediated antitumor activity [55]. Additionally, CDN-based STING agonists face significant challenges in intracellular delivery due to the negative electrophilicity and hydrophilicity of phosphodiester bonds, leading to rapid hydrolysis in circulation and tissues [108, 140]. Moreover, STING proteins are widely expressed in both tumors and normal tissues, raising concerns about specificity and potential side effects [69]. Therefore, combining STING agonists with other therapeutic agents may enhance treatment efficacy.

In summary, these findings highlight the dual roles of cGAS-STING signaling in tumor regulation, where immune-suppressive molecules such as PD-L1 and IDO are linked to STING activation. The activation of NF-κB and the production of the SASP contribute to tumor initiation and progression, enhancing our understanding of the interactions between cellular senescence and resistance to radiation and chemotherapy. These findings also partially explain the limited efficacy of STING activation in cancer therapy.

Conclusion

The cGAS-STING signaling pathway is a pivotal innate immune mechanism that plays a crucial role in cancer immunotherapy. STING agonists have been shown to directly induce tumor cell death, enhance antigen processing and presentation, promote T cell activation, and remodel the tumor immune microenvironment, thereby suppressing tumor growth [34, 141, 142]. Combining STING agonists with tumor vaccines and immune checkpoint inhibitors (ICIs) has been shown to significantly increase therapeutic efficacy in specific contexts [66, 73, 87]. This combination facilitates the conversion of "cold" tumors into "hot" tumors, activating preexisting antitumor T cell responses within the tumor and thereby increasing the effectiveness of STING agonists treatment [143]. However, the combination of STING agonists and immune checkpoint inhibitors poses certain risks. STING agonists are non-specific and can be activated by both tumor and normal cells, leading to the production of pro-inflammatory cytokines. When combined with immune checkpoint inhibitors, this effect may be amplified, potentially resulting in a cytokine storm. Additionally, the combination of STING agonists and immune checkpoint inhibitors could transiently activate T cells, potentially leading to autoimmune responses [144, 145]. In melanoma, the hypermethylation of the cGAS and STING gene promoters leads to coordinated transcriptional silencing, resulting in the significant impairment of STING signaling in both human melanoma samples and cell lines. The demethylation of these genes has been shown to restore STING activity, suggesting that combining STING activation with demethylation therapies could further increase the therapeutic efficacy of STING agonists [36]. Owing to the potent immunostimulatory effects of STING agonists, numerous novel compounds have been developed in recent years, with several currently undergoing clinical trials. However, the development of STING agonists faces several challenges. These challenges include the dual roles of STING signaling and issues related to the specificity and delivery of STING agonists, underscoring the need for ongoing research to address these hurdles. Furthermore, our understanding of the cGAS–STING pathway remains incomplete. For example, the mechanisms by which cGAS-STING signaling is suppressed in cancer remain incompletely understood. Similarly, the mechanisms by which STING activation induces the expression of immune-suppressive molecules, such as PD-L1 and IDO, remain unclear. Recent discoveries regarding the conformational regulation of the STING pathway revealed that the binding of cGAMP induces the closure of the ligand-binding domain, leading to a 180° rotation relative to the transmembrane domain. This conformational change is accompanied by alterations in the dimeric loop of the ligand-binding domain, resulting in the formation of STING tetramers and higher-order oligomers through side-by-side stacking [146]. However, the precise mechanisms through which these conformational changes regulate pathway activation warrant further investigation. Additionally, addressing the conflict between the site of action and the ubiquitous expression of STING remains an active area of research. It has been shown that delivery of CDN can be enhanced by poly beta -amino ester (PBAE) nanoparticles [68], which can improve the accuracy of STING action. In addition, new delivery modes should be developed to enable STING agonists to act more precisely at the target site and reduce adverse effects. In a recent trial, intramuscular injection of STING agonist in combination with anti-PD-1; anti-CTLA-4 significantly prolonged survival in pancreatic cancer model mice [147]. Therefore, reducing the dose of STING agonists in combination therapies to mitigate the risk of cytokine storms, improving the delivery system for precise targeting of tumor cells, and modifying STING agonists to enhance their stability are key strategies for the future development of these agents. We anticipate that with further research, the limitations of STING agonists will be addressed, facilitating their more effective application in cancer therapy.

Abbreviations

DNA	Deoxyribonucleic acid
cGAS	Cyclic GMP-AMP synthase
STING	Stimulator of interferon genes
IRF	Interferon regulatory factor
NF-κB	Nuclear factor kappa-B
TLR9	Toll-like receptor 9
AIM2	Absent in melanoma 2
IL	Interleukin
cGAMP	Cyclic GMP-AMP
ER	Endoplasmic reticulum
TBK1	TANK-binding kinase 1
IKK	Inhibitor of kappa B kinase
IκB	Inhibitor of NF-κB
IFN	Interferon
TNF	Tumor necrosis factor
IFNAR	IFN-α receptor 1
JAK	Janus kinase
TYK	Tyrosine kinase 2
STAT	Signal transducer and activator of transcription
ISGF3	Interferon-stimulated gene factor 3
ISRE	Interferon-stimulated response element
TME	Tumor microenvironment
ECM	Extracellular matrix
DC	Dendritic cell
APC	Antigen-presenting cell
MHC	Major histocompatibility complex class
TCF1	T Cell factor-1
VCAM	Vascular cell adhesion molecule
ICAM	Intercellular adhesion molecule
CTL	Cytotoxic T lymphocyte
NKG2D	Natural killer group 2 memberd
RAE1	Ribonucleic Acid Export 1
MDSC	Myeloid-derived suppressor cell
SLC	Solute carrier
TAM	Tumor-associated macrophage
PARP	Poly ADP-ribose polymerase

BRCA	Breast cancer susceptibility gene
APC	Antigen-presenting cell
TAA	Tumor-associated antigen
CDN	Cyclic dinucleotide
GM-CSF	Granulocyte-macrophage colony-stimulating factor
LNP	Lipid nanoparticle
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death-Ligand 1
CTL	Cytotoxic T lymphocyte; PBAE: poly(β-amino ester)
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
ICI	Immune checkpoint inhibitors
KSHV	Kaposi's sarcoma-associated herpesvirus
SCFV	Single-chain variable fragment
ABZI	Aminobenzimidazole
IDO	Indoleamine 2,3-Dioxygenase
HCC	Hepatocellular carcinoma
ROS	Reactive oxygen species
DSB	Double-strand break
DDR	DNA damage response
SASP	Senescence-associated secretory phenotype

Author contributions
Mengzhou Shen, Xianjie Jiang, Qiu Peng, Linda Oyang, Zongyao Ren, Jiewen Wang, Mingjing Peng and Yujuan Zhou collected the related paper and drafted the manuscript. Qianjin Liao and Xiyun Deng participated in the design of the review and draft the manuscript. All authors read and approved the final manuscript.

Funding
This work was supported in part by grants from the following sources: the National Natural Science Foundation of China (82202966, 82472882, 82302987, 82303534, 82203233, 82173142), the Natural Science Foundation of Hunan Province (2025JJ30047,2024JJ4025, 2024JJ6287, 2023ZJ1122, 2023JJ60469, 2023JJ40413, 2023JJ30372, 2023JJ30375), Science and Technology Innovation Program of Hunan Province (2024RC3231, 2023RC3199, 2023SK4034, 2023RC1073), the National Key Clinical Specialty Scientific Research Project (Z2023086, Z2023017), the Hunan Provincial Health High-Level Talent Scientific Research Project (R2023040, R2023093), the Research Project of Health Commission of Hunan Province (202203034978, 202202055318, 202109031837, 202109032010), Key Research and Development Program of Hunan Province (2022SK2051), Ascend Foundation of National cancer center (NCC201909B06), and by Hunan Cancer Hospital Climb Plan (ZX2020001-3, YF2020002, 2023NSFC-A001, 2023NSFC-A002, 2023NSFC-A004).

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

Declarations

Ethical approval
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 23 December 2024 / Accepted: 17 March 2025
Published online: 05 April 2025

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