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Deciphering the Double-Edged Action of STING pathway in Cancer

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Abstract

Cancer cells have unstable chromosomes and damaged DNA, which can activate the cellular alarm system cGAS-STING. This mechanism detects DNA in the incorrect location (the cytosol) and produces type I interferons, which can recruit immune cells to combat cancer. However, certain tumours can bypass or use this mechanism for their own benefit. This short article examines how cGAS-STING influences the different cells of the tumour microenvironment (TME), and how it can have both anti-tumour and pro-tumour effects. It also demonstrates how additional STING signals can cause inflammation and contribute to cancer growth. To employ cGAS-STING against cancer, it is critical to understand its complexities in various cell environments.

Keywords: cGAS-STING signalling, cancer, immune system, molecular biology, cancer immunotherapy

DNA Detection Mechanisms in Cancer

The immune system can recognize and destroy cancer cells, even though they originate from our own body. This is because these cells, especially those with many mutations, produce neo-

antigens that are detected by the adaptive immune system [1]. However, for the immune system to work effectively, it needs a favourable tumour microenvironment (TME), which should support the innate immune mechanisms that secrete interferons, cytokines and chemokines. These molecules attract and activate immune cells that fight cancer. One key innate immune mechanism is the STING (Stimulator of Interferon Genes) pathway, which is triggered by the cGAS (cyclic GMP-AMP synthase) sensor when it finds cytosolic DNA or DNA damage [3]. Pathogen-associated molecular patterns (PAMP) or the cell's own nuclear or mitochondrial DNA (DAMP) can both produce cytosolic DNA when damaged. Cancer cells frequently carry cytosolic DNA due to chronic DNA damage and chromosomal instability (CIN), which are hallmarks of cancer [4]. CIN and DNA damage can cause the creation of micronuclei, which contain damaged DNA or chromosomes. When these structures break, DNA is released into the cytosol [5]. CIN and DNA damage can also cause DNA fragments to leak from the nucleus or create chromatin bridges, which are detectable by cytosolic DNA sensors [6]. The cGAS-STING pathway is the primary method for sensing cytosolic dsDNA in a variety of cells, including during infection, malignancy, and DNA damage [4]. cGAS detects dsDNA with no sequence preference and produces ladder-like structures in the cytoplasm [7]. In the nucleus, where cGAS is also present, chromatin-bound nucleosomes impede its enzymatic activity [8]. However, cGAS may still interact with DNA replication forks, influencing genomic stability and homologous recombination [9]. When cGAS interacts with cytosolic dsDNA, it generates 2'3'-cyclic GMP-AMP (cGAMP), a second messenger that activates STING, an ER membrane protein [2, 10]. STING travels from the ER to the Golgi through the ER-Golgi intermediate compartment (ERGIC) and recruits TANK-binding kinase 1 (TBK1), which phosphorylates STING, interferon regulatory factor 3 (IRF3), and nuclear factor kappa-light-chain-enhancer of activated B cells

(NF-κB) [11]. These transcription factors activate interferon type I (IFN-I), cytokines, and chemokines such C-X-C motif chemokine ligand 10 (CXCL10) and C-C motif chemokine ligand 5 (CCL5). STING can potentially cause autophagy, senescence, or cell death, depending on the signal amplitude and cell type [12]. The cGAS-STING pathway is controlled by a variety of post-translational changes, including ubiquitylation, ubiquitin-like proteins, and metabolites [13].

STING Pathway Dynamics in Carcinoma Cells

STING can be triggered by extracellular cGAMP, bacterial cyclic dinucleotides (CdNs), membrane fusion, nuclear DNA damage, and cGAS, which generates cGAMP as a second messenger [2, 14]. IFN-Is and chemokines are produced as a result of STING activation, and these molecules alter the TME and the adaptive immune response [15]. In animal models, STING signalling has anti-cancer properties that can be augmented by STING agonists or cancer treatments like radiation [16]. By detecting their own DNA or by transferring cGAMP to nearby cells like stromal or endothelial cells, cancer cells can activate STING [17]. Angiogenesis and vascular normalization in tumours are likewise regulated by STING activity in the endothelium (Figure 1) [18].

Extracellular DNA from tumours in the TME activates the DNA sensing pathway when it is absorbed by immune cells, particularly the dendritic cells (DCs) [19]. DNA-vesicle fusion or chromatin proteins like high mobility group box 1 (HMGB1) may be involved in the processes of DNA absorption [20, 21]. When cGAS enters the cytosol, it starts to produce IFN-I, which is mostly produced by CD11c+ DCs in mice [22]. Anti-tumour immunity is induced by IFN-Is by improving DCs and antigen presentation to CD8+ T cells [2, 23]. Mice lacking the IFN-I receptor or STING in DCs lose this immunity and are unable to reject tumours [23, 24]. In

addition, STING decreases myeloid suppressors, activates NK cells, polarizes macrophages to the M1 phenotype, and uses chemokines to draw in more immune cells [25, 26, 27].

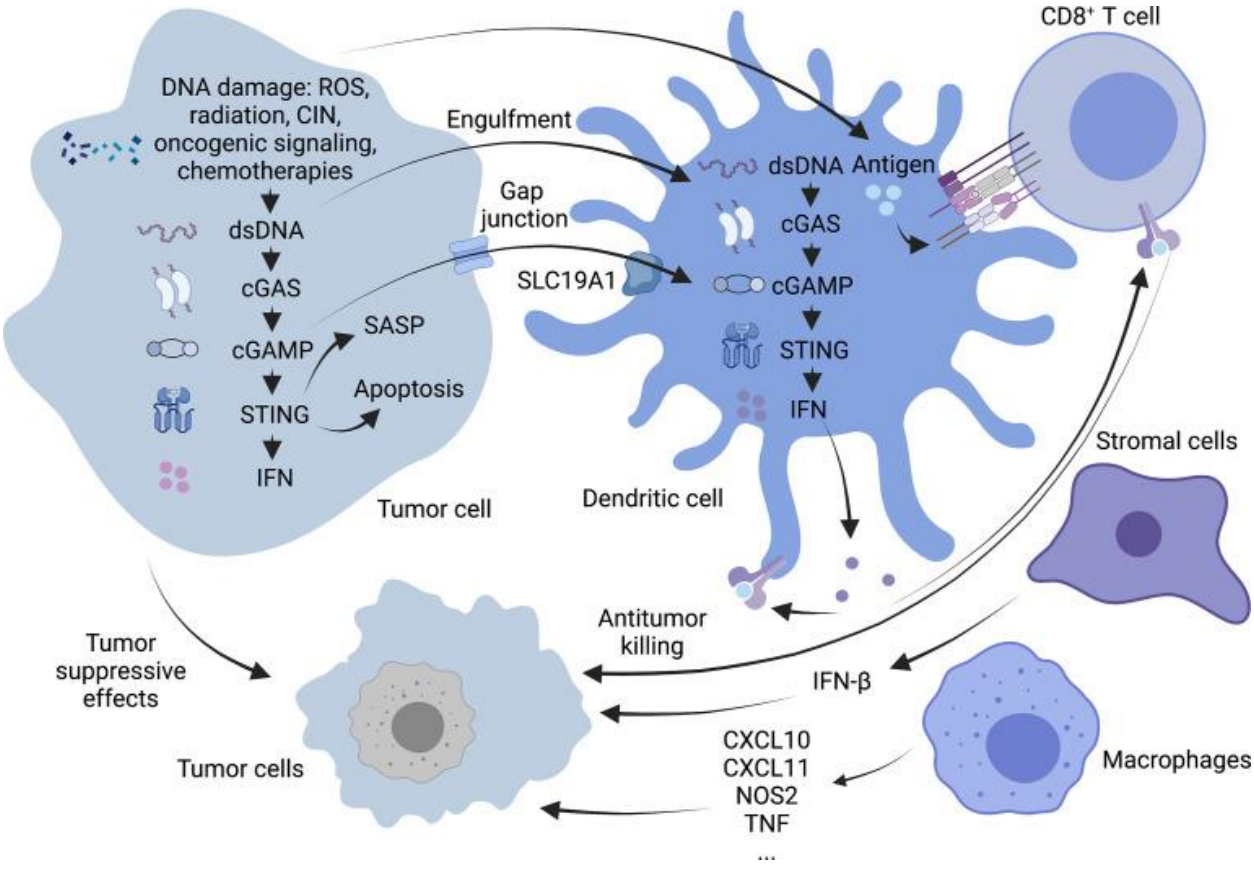

Figure 1: An Overview of Cellular Interactions in the Tumour Immune Microenvironment. The illustration portrays cellular interactions during an immune response against tumour cells. Various cell types, including tumour cells, dendritic cells, CD8+ T cells, stromal cells, and macrophages, participate in this complex process. Tumour cells experience DNA damage (due to factors like ROS and radiation) and undergo apoptosis. Dendritic cells engulf apoptotic tumour cells, while the cGAS-STING pathway activation leads to interferon (IFN) production. CD8+ T cells engage in antitumor killing activities, interacting with stromal cells. Key molecules like CXCL10, CXCL11, nitric oxide synthase 2 (NOS2), and tumour necrosis factor (TNF) play crucial roles in orchestrating this immune response. Image credits: Gan, Y, et al., (2022). [28]

Exploring STING Agonists as Soldiers in the Anti-Cancer Arsenal

STING signalling is a key feature of 'hot' tumours, which have DCs and cytotoxic T cells that can detect tumour antigens and respond to immunotherapy [2]. Thus, STING agonists have been investigated as potential anti-cancer therapies, including cGAMP, other cyclic di-nucleotides, and small compounds. They have shown impressive anti-tumour actions in mice models, which result in the removal of tumours and defence against recurrence [16]. Certain malignancies may produce enzymes that break down cytosolic DNA or cGAMP [30], or they may have malfunctioning or suppressed STING or cGAS genes [29], which would prevent immune recognition and activation. Tumour development is inhibited by IFN-I production and cell death that are triggered by acute STING activation [31]. On the other hand, persistent low-level IFN-β signalling stimulates the un-phosphorylated interferon stimulated gene factor 3 (U-ISGF3) complex, which in turn triggers pro-tumour genes [32]. Through the recruitment of myeloid-derived suppressor cells, the upregulation of programmed cell death ligand 1/2 (PD-L1/2), and the expression of indoleamine 2,3-dioxygenase (IDO), chronic IFN-I signalling also contributes to low-grade inflammation and immune suppression in the TME [32]. The anti-tumour responses mediated by T cells and STING are hindered by these factors [31]. Moreover, pro-inflammatory cytokines, particularly interleukin 6 (IL-6), are induced by STING signalling and improve cancer metastasis and survival [33]. Nuclear DNA damage triggers a cGAS-independent mechanism of STING signalling that activates NF-κB p65, which drives the generation of IL-6 [34].

By changing cGAS–STING signalling, which typically recognizes DNA and initiates IFN responses, tumour cells might elude immune detection. Through non-canonical NF-κB activation via p52 and RelB, tumour cells release pro-inflammatory cytokines instead of IFNs [2, 35]. This decreases the effectiveness of radiation treatment by blocking the traditional STING-TBK1-IFN route [36]. IL-6 also inhibits STING signalling in prostate cancer cells. As a result, depending on

the cell type and environment, STING signalling can have both pro- and anti-tumour effects. By causing T cells to undergo apoptosis or regulatory B cells to produce IL-35, STING signalling can also damage adaptive immune cells [2, 37, 38]. The results of STING signalling in T cells are modulated by T-cell receptor engagement [38]. Lower dosages or more targeted use of STING agonists are recommended to get around these obstacles.

STING Agonist and Anti-Vascular Therapy in Tumour Anticancer Effects

As stand-alone cancer therapies, vascular disrupting agents (VDAs) like combretastatin A4 phosphate (CA4P) have demonstrated a limited level of success [39]. According to preclinical research, CA4P efficiently disrupts the vasculature of tumours, especially in resistant tumour cores, but its effects are constrained by the tumour rim's ability to revascularize and stimulate regrowth [40]. Consequently, in order to enhance results, CA4P has been paired with various treatments in clinical trials, including radiation, chemotherapeutic drugs like paclitaxel and carboplatin, and the anti- vascular endothelial growth factor (anti-VEGF) antibody bevacizumab [41, 42, 43]. These mixtures have shown improved treatment outcomes and high levels of tolerance. Recent research has investigated the use of immunotherapy in conjunction with CA4P. In preclinical models, Deng et al. demonstrated that the combination of CA4P and chimeric antigen receptor–T cells (CAR-T cells) greatly increased antitumor activity [44]. Furthermore, in resistant mouse mammary cancer models, Oxi4503, an equivalent of CA4P, has been demonstrated to enhance responsiveness to immune checkpoint inhibitors [45]. The anticancer effects of combining CA4P with the immune-stimulating STING agonist cGAMP in order to lessen the side effects of STING agonists are discussed in a research by Czapla et al. [46]. Type I interferons and other proinflammatory cytokines are released with activation of the cGAS-STING pathway, which stimulates a potent antitumor immune response [46]. While a number of

STING agonists have been studied with varying degrees of success in preclinical and clinical settings, the Czapla et al. research is the first to look at the combined therapy of cGAMP and CA4P [46]. It was shown that while STING activation alone was adequate to prevent tumour development in B16-F10 tumours, there was no further advantage from CA4P, in the combination when it came to 4T1 cancers.

High STING expression in tumour and endothelial cells is expected to contribute to a successful antitumor response, as demonstrated by Demaria et al., who identified endothelial cells as the predominant source of type I interferon after cGAMP injection [47]. However, in 4T1 tumours, STING activation alone did not provide a significant immune response for long-term anticancer effects. Given the possibility of epigenetic silencing of cGAS or STING in many malignancies, combining CA4P with a vascular-disrupting drug was a sound strategy for highly vascularized 4T1 tumours [48]. This combination uses CA4P's vascular-disrupting capabilities to boost the antitumor response via cGAS-STING activation. STING agonists administered intra-tumourally stimulate innate immune pathways and counteract immunosuppressive settings, hence improving anticancer responses in non-immunogenic malignancies. The processes underlying the repolarization of the suppressive TME are still not well understood, despite the preclinical models' demonstrated effectiveness. Combination treatment successfully repolarizes macrophages from the immunosuppressive M2 phenotype to the immune-stimulatory M1 phenotype in both of the tumour models that have been investigated, as shown by Czapla et al. [46]. Tumour-associated macrophages (TAMs) of the M2-type predominate in the TME are known as "cold" TAMs, whereas those of the M1-type are known as "hot" TAMs [49]. The anticancer effects of STING signalling depend on macrophages changing from an M2 to an M1 phenotype [50]. Additional research supports the idea that STING agonists might repolarize

tumour-infiltrating macrophages, so transforming a "cold" TME into a "hot" one. Ohkuri et al., for example, have demonstrated that pro-inflammatory macrophages that are CD11b+Ly6C high, are recruited to the tumour in a STING-dependent manner [51], while Ager et al. have highlighted the role of STING agonists in repolarizing suppressive myeloid populations in both mice and humans, thereby enhancing immunotherapy efficacy [52].

Studies indicate that STING-activated and tumour-accumulating repolarized macrophages play an important role in the anticancer effects of STING-activating drugs. They further show that the use of STING agonists elicits a strong antitumor response in a variety of cancer models, which is predominantly mediated by natural killer cells (NK). Activation of the STING pathway overcomes immunotherapy hurdles such as immune exclusion and fatigue, making it a viable option for cancer eradication [53]. Consistent with these findings, Czapla et al. revealed that STING agonist treatment efficiently induces NK cells to target and eliminate tumours, with the therapeutic benefit reduced when NK cells are depleted, emphasizing their crucial role in anticancer therapy [54]. TAMs are known to affect NK cell activity and phenotypic. Specifically, TAM M2 macrophages strongly limit NK cell activation and cytotoxicity against tumour cells. Modulating the TME with IL-12 and anti-TGFβ increases the maturity and activation indicators of tumour-associated NK cells [46]. The process by which NK cells destroy cancer cells is reliant on the lack of major histocompatibility complex I (MHCI) molecules. NK cells recognize and kill cells missing MHC I molecules, successfully eradicating MHC I-deficient cancer cells in B16-F10 tumours. In MHC I-positive 4T1 tumours, NK cells may destroy cancer cells by many mechanisms, including the overexpression of stress-associated chemicals that function as ligands for NK activation receptors. These increased ligands enable NK cell activation by bypassing

MHC class I-dependent inhibition, resulting in the direct killing of tumour cells or the indirect release of pro-inflammatory cytokines [55].

The CD8+ T-cell response has long been thought to be responsible for STING therapy's antitumor effects. However, in the study conducted with the 4T1 breast cancer model by Czapla et al., an increase in tumour-infiltrating CD8+ T cells (TILs) following therapy was not observed. In contrast, melanoma models, particularly those with cGAMP injection, showed a considerable infiltration of CD8+ T cells. This resulted in melanoma tumours becoming "hot" infiltrated-inflamed tumours, with high amounts of TILs expressing the immune checkpoint receptor programmed cell death protein 1 (PD-1) [49]. Czapla et al. found that CD8+ T lymphocytes entering tumour tissues express CD69, which is associated with PD-1 expression [46]. CD69, an early activation marker for leukocytes, is known to be expressed on resident memory T cells, playing a vital role in the recruitment and retention of T cells in inflamed tissues. Several studies have highlighted CD69's role in producing tumour-infiltrating T cell fatigue. For example, Mita et al. found that tumour development and metastasis were reduced in Cd69-/- mice, which was connected to enhanced T-cell infiltration and decreased CD8+ T-cell fatigue [56]. The tumour models studied were characterized as low immunogenic "cold" cancers, which are usually resistant to immune checkpoint inhibitors (ICI-resistant tumours) [57]. STING agonist therapy has been demonstrated to boost the inflow of tumour-infiltrating CD8+ T lymphocytes, transforming immunologically "cold" tumours into "hot" cancers that respond better to ICI treatment. CD8+ T cells are critical for the efficiency of PD-1 inhibition; nevertheless, the presence of MHC I molecules on tumour cells is a required requirement for successful ICI treatment [58]. MHC I molecules are ligands for T-cell receptors (TCRs), and their recognition leads to T-cell activation.

The B16-F10 melanoma model, which lacks MHC I, showed a significant increase in CD8+ T cell infiltration into the tumour with exposure to cGAMP. An effective response to ICI therapy was seen when PD-1 blocking was explored in this setting, with some instances showing total tumour remission. This result might be explained by the overexpression of MHC I on B16-F10 tumour cells brought on by interferon γ (INFγ), which is generated by immune cells that have been activated by cGAMP, such as NK cells [46]. On the other hand, resistance to PD-1 treatment was shown in 4T1 MHC I-positive tumours. After STING activation, there was not a substantial inflow of CD8+ T cells, and these cells did not show higher levels of PD-1. Research has demonstrated that anti-PD-1 therapy is unable to produce antitumor effects in mice lacking cGAS or STING. This implies that before using STING agonists in conjunction with ICIs, patients may need to be screened for cGAS-STING signalling [59]. When ICIs are used in conjunction with cGAMP in tumour models where the cGAS-STING signalling pathway is functional, the effectiveness of the combination is markedly increased.

Conclusions

DNA sensing pathways, such as the cGAS–STING–interferon axis, are crucial for immune responses against infection, autoinflammation and cancer. However, STING signalling has complex and contradictory effects on tumour growth and suppression. STING agonists have failed to show anti-tumour efficacy in clinical trials, despite their success in mouse models.

Till date about 12 clinical trials have been focused on STING agonists, including compounds like ADU-S100, E7766, and GSK3745417 (Table 1) [60]. These agents hold promise for treating solid tumours and lymphoma. However, their cytosolic delivery remains a challenge due to inherent properties such as negative charge and hydrophilicity.

Table 1: The list of STING agonists confirmed for clinical trials [60]

Agonists	Treatment modality	Company	Administration method	Indications	Current status	NCT code
ADU-100	Combined with anti-CTLA4 mAb	Aduro Biotech; Novartis	Intratumoral injection (i.t.)	Advanced/metastatic solid tumours; lymphoma	Phase I (terminated)	NCT02675439
ADU-100	Combined with anti-PD-L1 mAb	Novartis	i.t.	Advanced solid tumours; lymphoma	Phase Ib (terminated)	NCT03172936
ADU-CL-20	Combined with anti-PD-L1 mAb	Aduro Biotech	i.t.	Metastatic/recurrent head and neck squamous cell carcinomas	Phase II (ongoing)	NCT03937141
BMS-986301	Monotherapy/combined with anti-PD-L1	Bristol-Myers Squibb	i.t.	Advanced solid tumours	Phase I (ongoing)	NCT03956680

	mAb or anti-CTLA4 mAb					
DMXAA	Combined with carboplatin and Paclitaxel	Antisoma; Novartis	Intravenous injection (i.v.)	Non-small cell lung cancer	Phase III (terminated)	NCT00662597
E7766	Monotherapy	Eisai Inc.	i.t.	Advanced solid tumours; lymphoma	Phase Ia/Ib (ongoing)	NCT04144140
E7766	Monotherapy	Eisai Inc.	i.v.	Bladder cancer	Phase I (ongoing)	NCT04109092
GSK3745417	Monotherapy/combined with anti-PD-L1 mAb	GSK	i.t.	Advanced solid tumours	Phase I (ongoing)	NCT03843359
IMSA-101	Monotherapy/combined with anti-PD-L1 mAb	ImmuneSensor Therapeutics	i.t.	Advanced solid tumours	Phase I/IIa (ongoing)	NCT04020185

MK-1454	Monotherapy/combined with anti-PD-L1 mAb	Merck & Co	i.v.	Advanced/metastatic solid tumours; lymphoma	Phase I (ongoing)	NCT03010176
MK-2118	Monotherapy/combined with anti-PD-L1 mAb	Merck & Co	i.v.	Advanced/metastatic solid tumours; lymphoma	Phase I (ongoing)	NCT03249792
SB-11285	Monotherapy/combined with anti-PD-L1 mAb	Spring Bank Pharmeceuticals	i.v.	Advanced solid tumours	Phase Ia/Ib (ongoing)	NCT04096638

To address this, most clinical trials have opted for intra-tumoural administration. By directly targeting the tumour site, intra-tumoural injection achieves well-defined primary concentrations while minimizing systemic exposure and associated toxicities. In select cases, these STING agonists are also administered intravenously or subcutaneously. It is essential to understand how DNA damage from different treatments affects STING signalling. By modulating the balance of STING signalling outputs, we may be able to enhance its anti-tumour functions and reduce its pro-tumour effects.

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