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*Review*

# Decrypting the Crosstalk Mechanisms Between cGAS-STING and TBK1 Signaling Pathways in Cancer Immunotherapy: A Comprehensive Review

**Sakuntala Gayen, Ankita Parui, Amima Arshad, Nipa Roy, Asmita Nag Sarkar, Souvik Roy***

Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata-Group of Institutions, West Bengal 700053, India

*Corresponding author: Souvik Roy, souvikroy35@gmail.com

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**Abstract**

In the tumor microenvironment, the cytosolic DNA sensing, cyclic GMP-AMP synthase- stimulator of interferon genes (cGAS-STING) pathway is a crucial regulator of immune response. The cGAS of innate immunity recognizes cytoplasmic DNA by catalyzing cyclic GMP-AMP (cGAMP), which subsequently activates the STING pathway. STING activation leads to the phosphorylation of TANK-binding kinase 1 (TBK1) and recruitment of key transcription factor IRF3, notably to initiate the production of pro-inflammatory cytokines and Type I IFNs. This cascade enhances antigen presentation and primes cytotoxic T-cells, leading to the induction of anti-tumor immune response. Specific crosstalk mechanisms, such as TBK1-mediated negative feedback to limit excessive STING activation or its cooperation with NF-κB to balance immune responses, play pivotal roles in shaping tumor immunity. Harnessing this axis in cancer immunotherapy has emerged as a promising strategy, offering synergy with immune checkpoint blockade and CAR T-cells therapy. Fine-tuning activation of this pathway is crucial for balanced immune responses, making cGAS-STING/TBK1 signal transduction a major target for novel cancer therapies. This review elucidates the intricate crosstalk mechanisms of cGAS-STING and TBK1 signal transduction within tumor microenvironment. These may shed insight on cancer therapy options and their pivotal roles in modulating tumor immunity.

## 1. Introduction

One of the most-deadly, life-threatening illnesses in the world is cancer. According to the GLOBOCAN database, an estimated 20 million new cases and 9.7 million deaths in the year 2022 [1]. Cancer is a genetically driven disorder influenced by various factors. The cancerous proliferation is commenced by the mutations of oncogenic drivers. Oncogenic protein mutations enhance the genetic variation and evolution rate of cancer cells, providing them with a selective advantage in their population [2,3]. This variety may set cancer cells apart from healthy cells, which immune systems are more likely to identify as foreign invaders. Cancer immunotherapy has been a major advance in the treatment toolbox for oncology due to immune activation. Chemotherapy, radiation, and surgery continue to be the mainstays of the traditional therapeutic strategy, but they significantly reduce patient survival rates [4-6]. With the recent development of our knowledge of tumoral immunity, immunotherapy has evolved into a potent new tool in the fight against carcinogenesis.

In the 20th century, the idea of cancer immunotherapy reappeared and acquired substantial momentum with the introduction of new technologies associated with immune system stimulation [7]. The immune system maintains the defensive mechanism against the foreign antigens and self-antigens by balancing immune activation and suppression. Fundamentally, this procedure encompasses the receptor - ligand binding among the antigens and various immune cells to modify T-cells activation, that simplifying the development of tumorigenesis and anti-tumor immune response [8,9]. Intriguingly, tumor microenvironment actively induces T-cell tolerance, resulting in an immunosuppressive action that facilitates tumoral recurrence and progression [10,11]. The latest study has indicated that numerous cancers suppress native immune responses by hindering effective anticancer immunity, as demonstrated through findings of reduced lymphocyte counts, T-cells apoptosis, exhaustion and anergy formation, down-regulation of antigen presentation in tumors, and enhanced proliferation of Tregs (regulatory T-cells) and tumor-associated macrophages [12]. In tumor immunology, strategic efforts have focused on developing immunotherapy that target the intricate relationships among the tumors and immune responsive cells. Cancer immunotherapy explores the impact of radiation treatment and modern cytotoxic chemotherapy on host immune systems, grounded in a deep understanding of the cancer-immune system interaction. In recent eons, a significant advancement has been developed in different immune-based treatments, comprising immune checkpoint blockade (ICB) therapy, adoptive cell therapy through CAR T-cells and CAR-NK cells therapies, administration of specific cytokines, and cancer vaccines, as new paradigm of cancer armamentarium [13-15]. The most widely used of these as an efficient treatment for various solid tumors and hematological malignancies is

immune checkpoint inhibitors (ICIs). ICB therapy is associated by immune checkpoint inhibitors as drugs which unleash effector T-cells activity via attenuating immune checkpoint such as cytotoxic T lymphocyte antigen - 4 (CTLA-4)/B7 and programmed cell death - 1 (PD-1) / ligands (PD-L1/PD-L2) interactions, situated onto the cell membrane of T-cells and tumor cells [16]. Moreover, adoptive cellular treatments are based on the patient's body being infused with immune cells that attack tumors. Cytokine treatment includes the infusion of immunomodulatory cytokines to stimulate the immune system, and cancer vaccines might be created to give preventive or therapeutic efficacy [17].

An innate immunological sensor called cyclic GMP-AMP synthase (cGAS) is able to identify different cytoplasmic double-stranded DNAs [18]. In order to affect interferon stimulator genes (ISGs), Type 1 interferons (IFNs), and other pro-inflammatory cytokines production, cGAS interacts with STING and stimulates downregulatory pathways. This activation strongly enhances the host immune responses which aids in the suppression and elimination of tumors [19,20]. Recent evidence increasingly suggests that cGAS-STING pathway is meticulously allied with the onset, propagation, as well as retreat of tumor. cGAS-STING signaling exhibits pro-tumorigenic or antitumorigenic activity via modulating different stages of the tumor immune cycle. This modification augments tumor antigen release, antigen presentation, T-cell priming, activation, and trafficking as well as T-cell infiltration into tumor tissues, thereby augmenting immunogenic tumor cell death [21,22]. Furthermore, TBK1 (TANK-binding kinase 1) performs significant part in tumor immunology through its interaction with cGAS-STING pathway, that is a critical constituent for innate immunity. TBK1 is a key kinase of cGAS-STING pathway to facilitate downstream signaling processes via phosphorylation of IRF3 (interferon regulatory factor 3), thus leads to transcription of interferons and other immune modulators. In contrast, TBK1 and cGAS-STING pathway could lead to debilitate immune responses, that contributes to initiate immune evasion by tumors [23,24]. Moreover, cGAS-STING signaling pathway has emerged as a key mediator of inflammation, cellular stress and tissue damage. The extensive role of the cGAS-STING pathway lies in its ability to detect and modulate cellular responses to both microbial and host-derived DNA, which act as a universal danger-associated signal [25]. Recently, cGAS-STING pathway recognized as a crucial immune mediator for intracellular DNA sensing. Zhang and his colleagues reported that cGAS-STING pathway is integral for understanding the diverse cellular responses and potential therapeutic target for neurodegenerative diseases [26,27]. Additionally, cGAS-STING signaling can affect the progression of liver inflammation through other mechanisms like autophagy and metabolism, as resulting to facilitate innate immune modulation in different liver diseases [28]. Therefore, understanding the mechanism of cGAS-STING and TBK1 pathways in cancer immunotherapy is essential for optimizing and developing novel therapeutic strategies to overcome resistance mechanisms. This review article sheds light on the interplay mechanisms of cGAS-STING and TBK1 signal transduction in cancer immunotherapy, aiming to offer guidance for investigating novel cancer immune mechanisms and therapeutic strategies, particularly through the development of selective inhibitors targeting cGAS-STING, and TBK1 pathways.

## 2. cGAS- STING Pathway: Molecular Mechanism

### 2.1 Structural Biology of cGAS-STING

cGAS, an approximately 520 amino acid containing protein belongs to nucleotidyl transferase (NTase) superfamily made up of two catalytic domains [29,30]. One is an N-terminal positively charged domain that controls cGAS dimer stabilization and another is C-terminal catalytic domain required for enzymatic activity and a Mab21 domain for DNA binding. The Mab21 domain has two lobes separated by a wide gap: the N-terminal lobe with β sheets and α helices, and the C-terminal lobe with a helix bundle and a conserved zinc region. By using two step the c-GAS binds to the ATP and GTP simultaneously to form the end product 2’3’c-GAMP. In the first step utilizing ATP as donor and 2’-OH on GTP as acceptor, a linear dinucleotide, 5’-pppG (2’-5’)pA formed. Then, this intermediary product turns over into catalytic pocket during second step. AMP moiety at acceptor and GTP moiety at donor position are engaged by the 3'–5' phosphodiester bond [26]. Cytosolic double-stranded DNA (dsDNA) is detected through cGAS and form cGAS - dsDNA complex, each molecule of cGAS is bound with two molecules of dsDNA via the primary and secondary binding site. The DNA sugar-phosphate backbone binds to Site A, the main DNA-binding site in cGAS, causing a conformational change. Site B, made up of many surface-exposed loops and a helix is important for cGAS signaling (Figure 1A) [31].

STING, a 40 kDa tiny protein present in endoplasmic reticulum (ER) membrane, has four transmembrane (TM) helices and N-terminal cytosolic portion [31]. The crystal structure of STING cytoplasmic domain is a highly organized hydrophobic dimer. In STING dimer there is a C-terminal tail (CTT) that binds to the TANK-binding kinase 1 (TBK1) essential for downstream signaling and a cytoplasmic ligand binding domain (LBD) which is crucial for promoting dimerization and cGAMP binding [30]. The four TM helices in the STING dimer are arranged into two layers: the perimeter, made by TM1 and TM3 and the centre layer, formed by TM2 and TM4. When 2’3’-cGAMP binds to LBD conformational changes occur. Following cGAMP-induced activation, CTT binds to TBK1 and cause STING-CTT phosphorylation. After phosphorylation, STING attracts IRF3, which is subsequently phosphorylates through TBK1. After that, the phosphorylated IRF3 dimerizes and translocate into nucleus and activates IFNs (Figure 1B) [31].

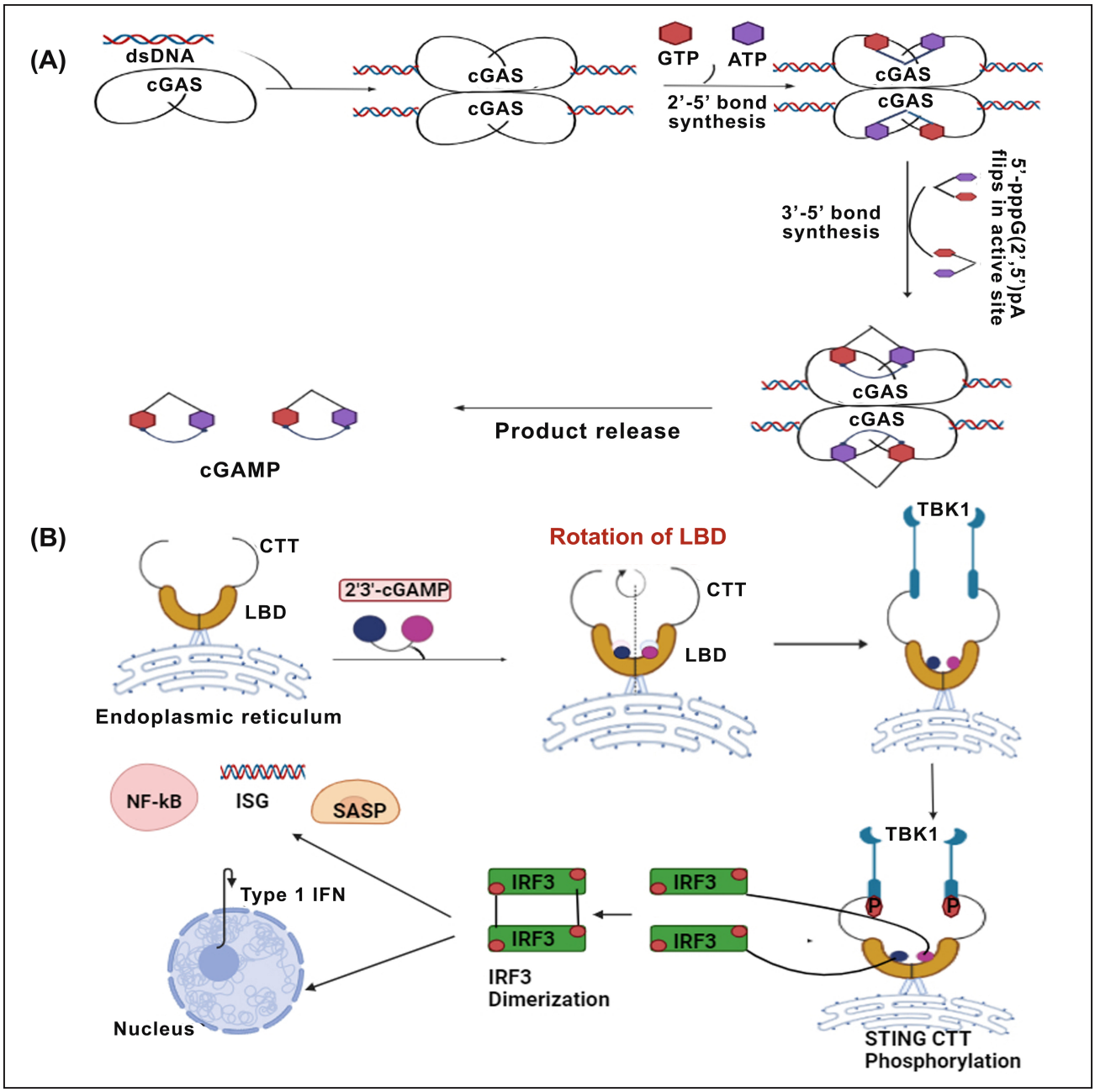


**Figure 1.** Structural biology of cGAS-STING. (A) production of cGAS and (B) activation of STING

### 2.2 cGAS-STING in Tumor Microenvironment

#### 2.2.1 cGAS-STING Stimulates the Growth of Tumors

The signaling pathway of cGAS-STING upregulates IFN production and promotes anti-tumor effects through innate immune responses, but in other studies it has been found that it can promote tumor development and induce carcinogenesis driven by inflammation [32]. The metastasis of human brain cells is linked to chromosomal instability (CIN) caused by improper chromosomal segregation during cell division. Through gap junctions, cGAMP produced by cGAS is transported to astrocytes, where it activates astrocyte STING and initiates the release of pro-inflammatory cytokines to support tumoral growth and survival of metastatic cancer cells in the brain (Figure 2A) [33]. The metastasis of human brain cells is linked to chromosomal instability (CIN), which caused by improper chromosomal segregation during cell division. In metastatic models, CIN promotes the growth of micronuclei and cGAS–STING signals eliciting non-canonical NF-κB signaling. CIN-driven metastasis is reliant on STING and NF-κB signal transduction, and it also correlates with the transition of epithelial to mesenchymal tissue and the activation of genes linked to inflammation [34]. Research on STING's function and mechanism in Lewis's lung cancer (LLC) demonstrated that abnormally high STING expression significantly promotes LLC growth and multiplication. When tumor cells are damaged by carcinogens, significant numbers of DNA are released inside the cytoplasm, which keeps STING signaling pathway active and encourage the synthesis of chemokines in the tumor cells. In order to promote the growth of tumors, these chemokines attract a lot of inflammatory cells, including immunosuppressive cells like M2 tumor associated macrophages (TAMs) and

myeloid derived suppressor cells (MDSCs). Studies showed that STING increases MDSCs proportion in mouse melanoma. As a result, treating these malignancies with STING agonists runs the risk of over-stimulating the STING signaling system and accelerating the growth of tumors (Figure 2A) [34].

### 2.2.2 cGAS-STING in Tumor Inhibition

Cytosolic DNA, produced by a number of DNA damage process, including oxidative stress, radiation, hyper activation of oncogene signaling, low chromosomal instability is widespread in cells constituting the tumor micro environment [33]. cGAS recognized abnormal exogenous and endogenous DNA in cytoplasm and produces an endogenous second messenger 2′3′ cyclic GMP-AMP (2′3′-cGAMP) which binds directly and activates STING, which in turn activates IFN response and produces pro-inflammatory cytokines (Figure 2B) [35,36]. When cGAMP attaches into a certain region on the STING dimer, STING is transported from the ER to perinuclear microsomes through Golgi apparatus [34]. The generation of type I IFN and senescence-associated secretory phenotype factors (SASP) is increased upon stimulation of the cGAS-STING pathway and promote the cell senescence. In tumor cell type 1 IFN triggers the apoptotic factors like caspase 9, caspase 3, Bax and ultimately cause apoptosis. Thus, stimulation of cGAS-STING pathway inhibits growth of cancer by causing cell senescence [32]. Tumor inhibition is mostly dependent on the cGAS-STING pathway, which is also active in dendritic cells (DC). DCs produce type I IFNs that primes CD8+ T cells against immunogenic malignancies (Figure 2B) [34]. Natural killer (NK) cells, which stimulate cGAS-STING signaling pathway and upregulate production of NKG2D ligand, are crucial components of STING-mediated anti-tumor immune responses, along with T cells and DCs. The binding of increased NKG2D ligands on the surface of tumor cells to NKG2D receptors on the surface of NK cells facilitates the killing of tumor cells by NK cells. The tumor microenvironment is largely composed of stromal cells that express STING genes, such as fibroblasts and endothelial cells. Apart from that cGAS-STING is also involved in cancer propagation alongside with its involvement in carcinogenesis and maturation. When STING is activated in cancer cells, the environment surrounding cancer is altered to cause cell death via NF-κB signaling, which effectively stops tumor migration and metastasis [32].

### 2.3 cGAS-STING in Immune Regulation

Tumorigenic cell clearance by the immune system first depends on production of type I interferon (IFN) by dendritic cell (DC) and the recruitment of CD8+ T-lymphocytes, thus encourage the targeted killing of such aberrant cells [35]. It was discovered by researchers through an unclear mechanism that tumor-derived DNA and cGAMP activate the cGAS-STING pathway in DCs, which in turn enables cross-presentation to DCs and engages CD8+ T lymphocytes for direct, non-spontaneous tumor eradication (Figure 2B) [37]. Type-I IFN, a key player in the STING pathway, is involved in the production of chemokines like CXCL9 and CXCL10, which are essential for cytotoxic T lymphocyte metastasis. This pathway also plays a role in immunosuppression of regulatory T cells [38]. DCs are thought to be able to accept tumor-acquired DNA or cGAMP through gap junctions or endocytosis. Following this, the expression of cell surface co-stimulator molecules is aided by the stimulation of the STING signaling pathway. Moreover, it improves DC antigen presentation and fosters DC maturation. Additionally, tumor cells, stromal cells, and immunological cells such T cells, macrophages, and NK cells express STING (Figure 2B) [32]. To eradicate tumors, NK cells require STING expression in tumor cells. Large volumes of IFNs are produced by activated immune cells, and these IFNs stimulate antitumor immunity by directly or indirectly interacting with IL5 and IL15 receptors in NK cells, ultimately killing tumor cells to create effects that decrease tumor growth [37]. STING-mediated autophagy may work in conjunction with canonical NF-κB signaling and IRF3 to prevent or inhibit the growth of cancer through an unidentified mechanism. Furthermore, the cGAS-STING pathway facilitates the regulation of antitumor immunity through interaction between immune cells and tumor cells [33].

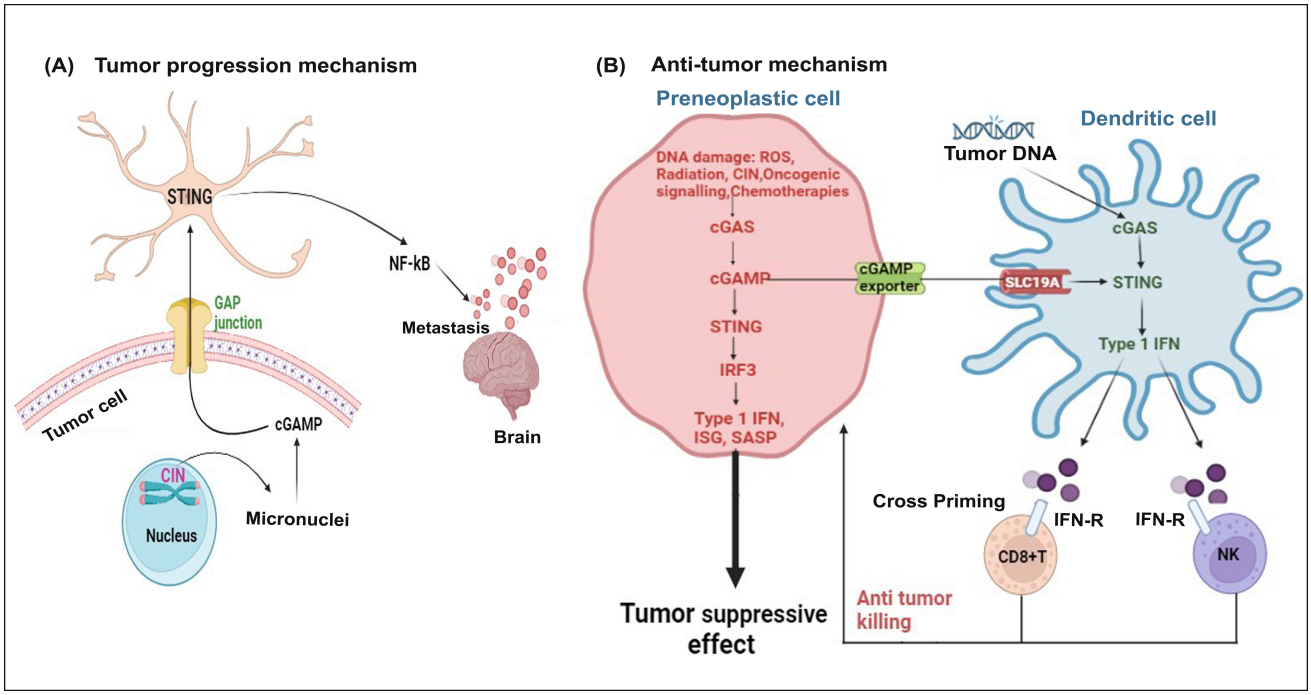


**Figure 2.** Dual mechanisms of cGAS-STING in tumor. (A) Tumor progression mechanism (B) Anti-tumor mechanism

## 3. TBK1 Signaling Pathway: Molecular Insight

### 3.1 Biology of TBK1

TRAF-associated NF-kB activator, or TANK Serine/threonine kinase binding kinase 1 is a 729 amino acid member of the nuclear factor-kb (IkB) kinase (IKK) family of non-canonical inhibitors [24]. TBK1 gene is located on chromosome 12 which is constitutively expressed in all tissues along with fibroblasts, skin, adipocytes, CNS (central nervous system) and cancer cells [39]. TBK1 contains four key domains: an N-terminal kinase domain (KD; residues 1-307), a ubiquitin-like domain (ULD; residues 308-384), and two coiled-coil domains (CCD1/SDD (scaffold/dimerization domain); residues 407-657 and CCD2; residues 658-713). The KD (kinase domain) is crucial for activating molecules like IRF3. It has two parts (N-terminal and C-terminal) with an active site in between, and phosphorylation of Ser172 in its activation loop changes its structure to allow binding [40,41]. The ULD regulates kinase activity by interacting with the KD and other proteins, and it plays a crucial role in maintaining TBK1's kinase activity. Conserved residues within the ULD, such as Leu316, Ile353, and Val382, are critical for protein-protein interactions, with mutations in this region potentially halting downstream signaling. TBK1 forms homodimers or heterodimers with IKKi through interactions involving the SDD/CCD1 domains, KDs, and ULDs. This dimerization is necessary for TBK1 activation and subsequent signaling. The CCD2 domain in the C-terminus contains an adaptor-binding motif that enable interactions with proteins like TANK, optineurin (OPTN), NAP1(NAK–associated protein), TBKBP1(TBK1-binding protein 1; SINTBAD) determining TBK1's subcellular localization and signaling specificity [41]. TBK1 activation can be regulated by Oncogenic kinases, inflammatory cytokines, pathogen-associated molecular patterns (PAMPs; released by invasive bacteria or viruses), damage-associated molecular patterns (DAMPs; released by injured tissues), including activated K-RAS/N-RAS mutants [24]. TBK1 integrates responses from a variety of extracellular and intracellular stimuli and regulates different signaling pathways by regulating expression of type I interferons (IFNs; IFN-α/β) transcription factors, interferon regulatory factors 3 and 7 (IRF3/7), while also participating in different biological processes like immunity, inflammation, autophagy, mitochondrial metabolism, specifically mitophagy and xenophagy, energy homeostasis and cell death [39,40].

### 3.2 TBK1 in Tumor Microenvironment

TBK1 have a very heterogenous role in the tumor microenvironment. TBK1 in cancerous cells drives tumor proliferation by activating key pathways involved in survival and proliferation, including MYC, JAK/STAT, p62/autophagy, NF-κB, and AKT-mTOR1. It also induces tumorigenic cytokines like IL-6, supporting autocrine cell survival. In KRAS-mutant cancers, TBK1 promotes survival by enhancing NF-κB and mTOR1 pathways, which prevent apoptosis and boost protein synthesis. TBK1 activates NF-κB by phosphorylating important regulators and supports tumor growth by interacting with the AKT-mTORC1 pathway to enhance mTORC1 signaling (Figure 3) [42]. Interestingly, TBK1 performs a dual function in immune regulation, sometimes promoting immune suppressive action and in other way enhancing immune responses. For instance, dendritic cell TBK1 deletion can improve antitumor immunity and T cell activation. While, in other contexts, TBK1 promotes an immunosuppressive environment by influencing cytokine production including IL-6, TNFα, IFNβ, and CXCL10 (IP-10) and T cell function. The STING-TBK1 pathway, crucial for activating CD8 T cells via dendritic cell priming, highlights TBK1's complex role in the immune response against tumors

(Figure 3). However, TBK1's role is context-dependent and varies across different cancers [43]. In prostate cancer, TBK1 inhibits mTOR signaling in bone marrow niches, contributing to cancer cell dormancy and resistance to conventional treatments. In contrast, in renal cell carcinoma (RCC) and breast cancer, TBK1 supports tumor survival and progression through pathways like autophagy and oestrogen receptor signaling. Through pre-metastatic niche TBK1 also interact with in situ tumors as well as distant metastatic tumors. Thus, through persistent inflammatory activation, the TBK1 pathway not only initiates tumor formation but also enhances anti-tumor surveillance [43].

### 3.3 TBK1 in Immune Regulation

TBK1, a key player in the innate immune system, activates type I interferons (IFN-α/β) in immune cells by phosphorylating IRF3 (at Ser386 and Ser396) and IRF7 (at Ser477 and Ser479). When phosphorylated IRFs attach to (ISRE) IFN-stimulated response elements in gene activators like IFNB and RANTES, leading to form dimers and translocate into the nucleus. TBK1 activates IRF3/IRF7 and NF-κB signaling through the STING pathway, leading to the production of inflammatory cytokines (IL-8, IL-1β, TNFα) and Type-1 IFNs. Additionally, TBK1 promotes proliferation by regulating genes involved in survival and proliferation, such as RelB, BCL-xL, Cyclin D1 and XIAP [44]. The adaptor protein STING (TMEM173) responds to dsDNA via the cGAS-STING pathway, producing the second messenger 2′3′-cGAMP, which triggers autophagy (Figure 3). The immune defence response against tumors is also activated by the NF-κB and IRF3 pathways. When paired with the IL-6R/JAK signaling pathway, this activation increases macrophage phagocytosis and triggers apoptosis. STING is essential for polarizing macrophages and produces IFN-β [45]. Several studies demonstrated that TBK1 reacts to signals from many receptors, such as B cell receptor (BCR), T cell receptor (TCR), and members of the TNF receptor (TNFR) super family, which maintain adaptive immune responses and homeostasis. In B cells, TBK1 prevents NF-κB activation by NIK phosphorylation, leading to its ubiquitin-dependent degradation and control IgA class switching [46]. TBK1 regulates dendritic cell function and T-cell homeostasis by controlling IFN-induced signaling. This function involves phosphorylation of STAT3 at serine 727, which negatively regulates gene expression and STAT1 activation caused by type-I IFN (Figure 3) [24].

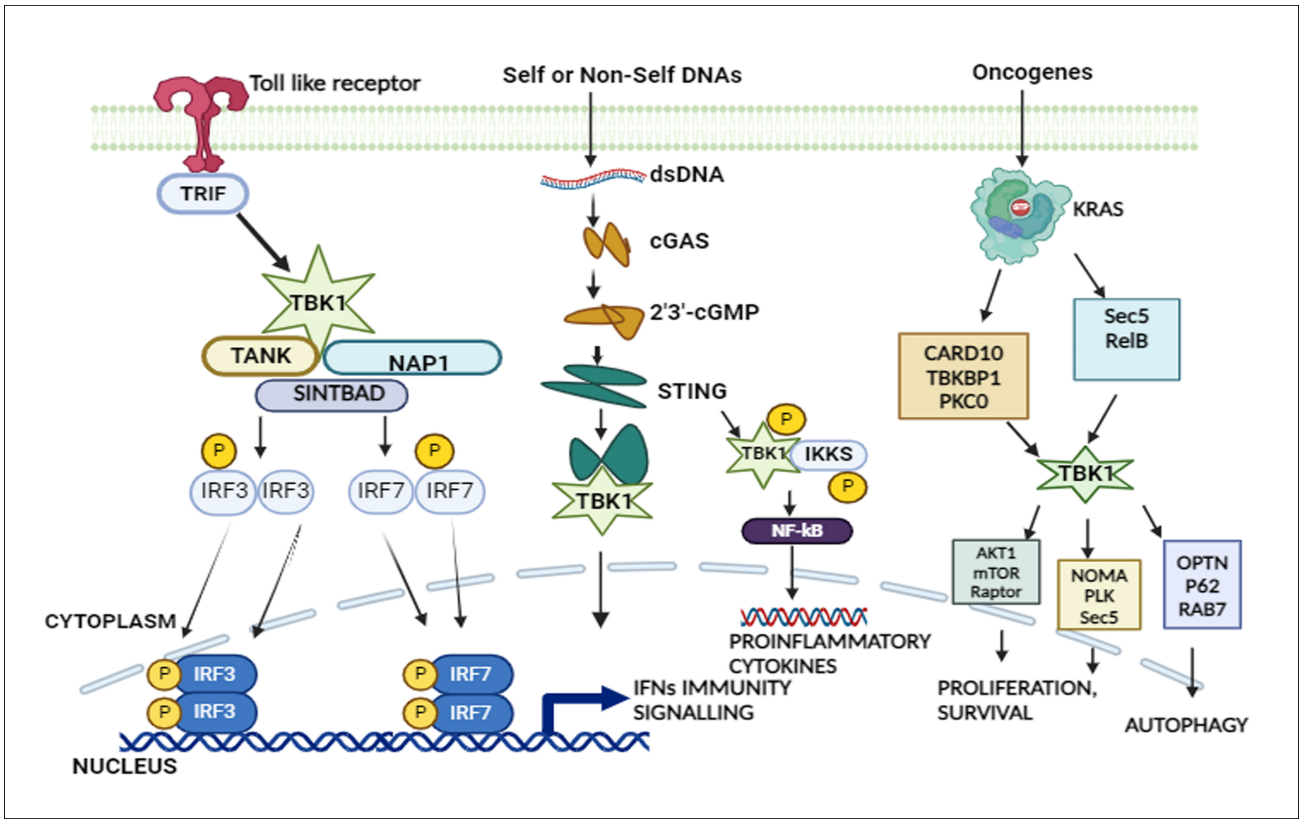


**Figure 3.** TBK1 role in tumor microenvironment and immune regulation

## 4. Crosstalk Mechanism of cGAS-STING and TBK1 Pathway in Tumorigenesis

The cGAS-STING pathway plays a pivotal role in detecting cytosolic double-stranded DNA (dsDNA), initiating immune responses that are critical in fighting cancer, infections, and inflammation. cGAS, upon binding to dsDNA, synthesizes cyclic GMP-AMP (cGAMP), a second messenger that activates the STING protein in ER. STING then translocates to the Golgi apparatus, where it undergoes modification like palmitoylation and recruit kinases such as TBK1. This cascade leads to the activation of interferon regulatory factor 3 (IRF3) and nuclear factor-kappa B (NF-κB), which regulate the expression of type-I IFNs and inflammatory cytokines to bolster immune defences [47].

The cGAS-STING pathway is a crucial cellular sensor for cytosolic double-stranded DNA (dsDNA) that supports innate immune responses to fight cancer and inflammation [48,49]. The stimulation of cGAS-STING pathway can be prompted by both intrinsic and extrinsic self-DNA sensing. Sequence-independent upstream contact between dsDNA and the cGAS enzyme causes cGAS to conformationally alter, which catalyzes the synthesis of 2C,3′-cyclic GMP-AMP (cGAMP), a cyclic dinucleotide made of phosphodiester linkage from both 2′-5′ and 3′-5′ [50-52]. The cGAMP unveiling as a second messenger which activates STING expression in ER, and subsequently translocate into Golgi apparatus to form tetramer by higher-order oligomerization (Figure 4) [53-55]. STING is Palmitoylated in the Golgi apparatus is significantly encouraged to facilitate the recruitment of TBK1 and interferon regulatory factor 3 (IRF3) [56,57]. In addition, tetramerization of STING stimulates and draws in TBK1 dimers, which then trans-phosphorylate STING at its C-terminal domains, activating IFR3. Subsequently, IFR3 translocation into nucleus drives the upregulation of immune stimulated genes (ISGs) and type-1 interferons production (Figure 4). This modulation improves the body's immune system's capability to detect and destroy tumor cells by stimulating dendritic cell development and increasing cytotoxic T-lymphocytes (CTLs) infiltration at targeted areas [58], thus improving the immune system's ability to identify and eradicate tumors. As an alternative, STING activation can also stimulate the production of nuclear factor-kappa B (NF-κB), a transcription factor essential for cell survival and carcinogenesis progression [59].

Conversely, the downregulation of cGAS-STING / TBK1 transduction often exploited by tumors to evade the immune response. Cancer cells could accomplish this signaling via the suppression of cGAS or STING expression, and promotion of negative regulators within cGAS-STING / TBK1 pathways [60]. The suppression of cGAS-STING / TBK1 transduction dampens the expression of type-I interferons, thereby weakens the immune systems to battle tumors, facilitating tumor progression and metastasis (Figure 4) [61,62]. Understanding the dynamic regulation of cGAS-STING-TBK1 axis in different tumors is critical for developing targeted therapies that can either enhance or restore their function, thereby improving the effectiveness of cancer immunotherapy. In cancer, this pathway is activated by the detection of abnormal DNA fragments from damaged or stressed cells, enhancing anti-tumor immunity through dendritic cell activation and T-cell recruitment. However, chronic activation of STING can sometimes promote tumor progression by inducing an inflammatory environment. Recent research has highlighted its dual roles and the development of STING modulators as potential therapeutic strategies [63].

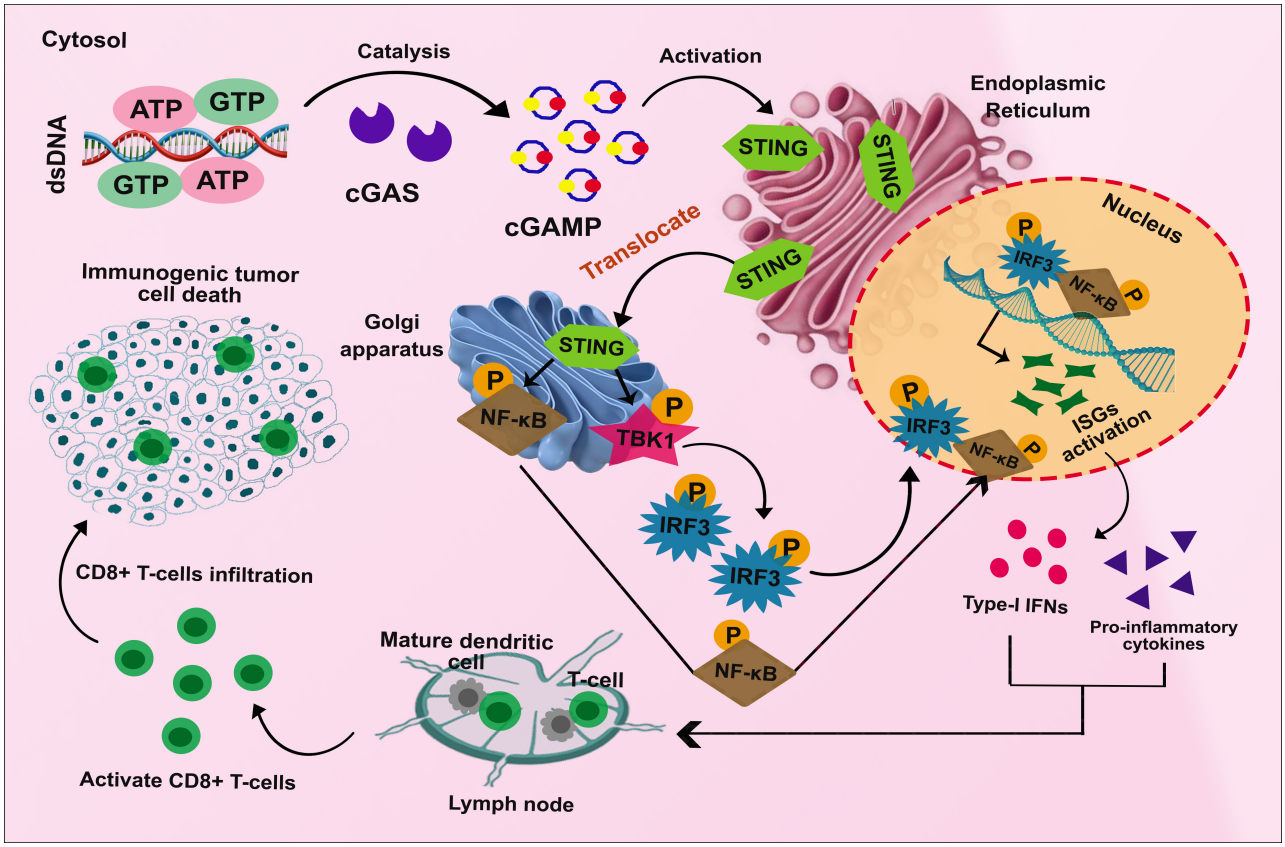


**Figure 4.** Crosstalk mechanism of cGAS-STING-TBK1 in cancer immunotherapy

## 5. Application of cGAS-STING/TBK1 Pathway in Cancer Immunotherapy

The cGAS-STING/TBK1 signal transduction is crucial in cancer immunotherapy by triggering innate immune responses against tumors. This pathway is initiated when cGAS detects cytosolic DNA from tumor cells which increases the generation of cGAMP, leading to activate STING in ER. Following stimulation, STING enlists and activates TBK1, which helps phosphorylate IRF3. This

activation facilitates the downregulation of the expression of type-I interferons (IFNs) and other pro-inflammatory cytokines that promote immune cells infiltration and enhance antitumor immune responses [64,65]. By engaging the cGAS-STING and TBK1 axis, cancer immunotherapy can boost tumor cell recognition via immune cells activation, facilitating immunogenic tumor cell death (Figure 4) [25,66]. However, cGAS-STING/TBK1 axis role in inducing immunogenic cell death and overcoming immune evasion has also made a potential biomarker for enhancing the efficacy of existing treatments [47,67], such as immune checkpoint inhibitors, CAR-T cells therapy, cancer vaccine, and oncolytic immunotherapy.

### 5.1 Application of STING in Cancer Immunotherapy

The appropriate adjuvant plays an important factor in overcoming tolerance and enhancement of immune responses in tumors, and innate immune system which leads to boost antigen presentation, it makes tumor-associated antigens (TAAs) more immunogenic [68], with both cancer cells secreting cyclic dinucleotides (CDNs) and granulocyte-macrophage colony-stimulating factor (GM-CSF), STINGVAX has emerged as the first STING based cancer vaccine [69,70]. Research on STINGVAX injection in B16 transplanted melanoma, demonstrated that STINGVAX is prominently reduced the tumor proliferation in dose dependent manner and increased T-cells penetration into tumor cells [71]. In addition, Miao and associates created and produced a successful STING-dependent cyclic lipid nanoparticle (LNP) adjuvant for the delivery of antigen-specific mRNA vaccines. Through the use of a one step-component procedure, this research team created several synthetic lipid structures. The STING pathway may be activated by the cyclic amino head group of lipids. Using this combinatorial LNP in a mouse model shown a significant increase in survival rate by activating STING and inducing antitumor immune responses [72].

Recently, several STING agonists have been utilized in clinical investigations as anticancer drugs, and STING/ICIs combinations also established [73]. STING signaling and type-I interferons play an important role in substantial T-cells action by cross-presents of CD8α+ DCs, influence intra tumoral T-cell infiltration [74]. Furthermore, using anti-CTLA-4 therapy can lower the threshold for T-cells activation. Harding and his research team observed that in the absence of STING, the combination of ionizing radiation and anti-CTLA-4 therapy failed to induce abscopal tumor regression and reduction of cytotoxic T-lymphocytes infiltration in tumors [75]. Similarly, Ager's group conducted a related study with comparable findings. Their outcomes demonstrated that the combination therapy of anti-PD-1, anti-CTLA-4 and agonistics anti-4-1BB persuade bilateral tumor suppression while STING agonist added, which remarkably intercept the bilateral tumors in 75% of mouse model. Moreover, the combinatory approach of CAR-T cells with cyclic di-GMP (cdGMP, a STING agonist) activates host antigen presenting cells (APCs) and lymphocyte responses, leading to effectively eliminate malignancies [76]. Although the precise processes by which the simultaneous release of STING agonist and CAR T-cells activate the host immune system remain unclear, this CAR-T/cdGMP combination reflected long-lasting antitumor immune responses.

### 5.2 Application of TBK1 in Cancer Immunotherapy

TBK1 is increasingly recognized for its role in cancer immunotherapy due to involve in multiple key pathways that influence tumor progression and immune responses. Serine/threonine kinase, TBK1 regulates Type-I-interferon responses and modulates inflammation, both of which help to activate the innate immune system [77]. Recent studies highlighted the dual mechanisms of TBK1 in cancer, such as initiation of antitumor immune responses by enhancing the stimulation of interferon stimulated genes, thus facilitating immune surveillance to target tumors. Additionally, it can also facilitate tumor progression and resistance to therapy through the modulation of different signaling pathways, including NF-κβ, and autophagy [43]. For instances, research by Zhang and his colleagues demonstrated that TBK1 inhibition can improve the efficacy of immune checkpoint blockade therapy by overcoming resistance mechanisms and promoting a more robust immune responses against tumors [23]. Furthermore, it has been shown by Sun and his colleagues that TBK1 is a gene involved in immune evasion. By sensitizing tumor cells to effector cytokine-induced cell death, targeting TBK1 can improve responsiveness to PD-1 inhibition. This work demonstrated that TBK1 targeting sensitizes tumors to immune challenge using patient-derived ex-vivo models and syngeneic mouse tumor models [78]. Based upon the recent research, targeting TBK1 could be promising strategy to improve outcomes in cancer immunotherapy by bolstering antitumor immune responses and overwhelming resistance to existing therapies.

## 6. Therapeutic Targeting cGAS-STING and TBK1

The understanding of innate immunity has expanded, with a focus on the recognition of cancer-encoded messages by pattern recognition receptors [71]. The cGAS-STING pathway is a key modulator of both innate as well as adaptive immunity in response to foreign DNA derived from pathogens. It is recruited and activated by the presence of dsDNA in the cytoplasm, which is converted into a second messenger, cGAMP, which binds to and activates STING. cGAS recognizes tumor-specific DNA fragments, such as those derived from chromosomal instability and genomic breaks [79]. There are several strategies to target cGAS-STING and TBK1 pathway in cancer treatment, including small molecule inhibitors, gene editing, STING agonists, and combination therapies (Table 1, 2, and 3).

**Table 1.** Small molecule inhibitors targeting STING.

| Small molecule inhibitors | Mechanisms | Affinity | References |
|---|---|---|---|
| H-151 | It binds covalently to Cys91 in hSTING preventing palmitoylation by STING stimulation which prevents the hSTING protein from assembling into multimeric complexes in golgi apparatus and suppresses downregulatory signals transduction | NA | [85] |
| SN-11 | It works in vivo as a potent inhibitor of cGAS/STING | NA | [86] |
| C-178 | It attaches covalently with Cys91 in mSTING protein to prevent palmitoylation by STING activation which prevents the protein from assembling into multimeric complexes at the golgi apparatus, attenuates downstream signals transduction | NA | [85] |
| C-176 | It binds covalently with Cys91 in mSTING protein, prevents palmitoylation by STING activation which prevents the protein from assembling into multiplexes at the golgi apparatus, obstructs downstream signals transduction | NA | [85] |
| C18 | Showed inhibitory effects due to the production of IFNβ generated via cGAMP | IC5068nM | [85] |
| EGCG | It selectively targets G3BP1 to efficiently suppress DNA-dependent cGAS stimulation and the release of type I IFNs | NA | [85] |
| Aspirin | It efficiently suppresses cGAS associated immune responses by directly acetylating cGAS | NA | [85] |
| Astin-C | It may prevent IRF3 from joining the STING signalosome, obstructing subsequent signaling cascades | Kd ∼ 53 ± 14nM | [85] |
| RU365 | It facilitates an active conformation via DNA-persuaded “open pocket”, cGAMP with cGAS, the key intermolecular interactions occur through pyrazole and benzimidazole of RU365 moderately binds with Tyr 421 and Arg 364 | NA | [87] |
| RU521 | It shows that the two chloro moieties inserted into the catalytic pocket of cGAS, it elevates the assembling surface with Tyr 421 and Arg 364 of residues in cGAS catalytic sites, prevent it from binding GTP and ATP | NA | [87] |
| J001 & G001 | These two compounds are potent than m-cGAS subsequently, based on both found compounds, they ran an optimization program for medicinal chemistry to increase h-cGAS activity and selectivity. | NA | [87] |

**Table 2.** STING agonists in clinical study for cancer therapy

| Drugs | Combination therapy | Indication (cancer type) | Phase | Status | Route | References |
|---|---|---|---|---|---|---|
| Ulevostinag (MK-1454) | Monotherapy or combined with pembrolizumab | Advanced/metastatic solid tumors or lymphomas | I | Completed | Intratumorally | [88] |
| Ulevostinag (MK-1454) | combined with pembrolizumab | Metastatic head and neck squamous cell carcinoma | II | Completed | Intratumorally | [88] |
| E7766 | Monotherapy | Advanced solid tumors or lymphomas | I | Completed | Intratumorally | [88] |
| MK-2118 | Monotherapy or combined with pembrolizumab | Advanced/metastatic solid tumors or lymphomas | I | Completed | Intratumorally | [88] |
| TAK-676 | Combined with radiotherapy and p embrolizumab | Non–small-cell lung tumor, triple-negative breast tumor, or squamous cell cancer of the head and neck | I | Recruiting | Intravenously | [88] |
| SB 11285 | Monotherapy or combined with pembrolizumab | Melanoma head and neck squamous cell cancer advanced solid tumors | I | Recruiting | Intravenously | [88] |

| | | | | | | |
|---|---|---|---|---|---|---|
| IMSA101 | Monotherapy or combined with immune checkpoint inhibitor (ICI) or immuno-oncology (IO) therapy | Advanced treatment-refractory malignancies | I / II | Recruiting | Intratumorally | [88] |
| GSK3745417 | Monotherapy | Myeloid malignancies such as acute myeloid leukaemia (AML) and high-risk myelodysplastic syndrome (HR-MDS) | I | Recruiting | Intravenously | [88] |
| BMS-986301 | Monotherapy or combined with nivolumab and ipilimumab | Advanced solid cancers | I | Active, not recruiting | Intratumorally, Intramuscular, or intravenously | [88] |

**Table 3.** Small molecule inhibitors targeting TBK1

| Small molecule inhibitors | Mechanistic pathway | Affinity | References |
|---|---|---|---|
| BX795 | Originally designed to be a moderately powerful inhibitor of 3-phosphoinositide-dependent protein kinase 1 (PDK1), this drug also exhibits significant activity against a variety of other kinases, such as mixed lineage kinase 1-3 (MLK1-3), IKKε, Aurora B, and MARK1e4 (AMP stimulated protein kinase 1-4) | NA | [87] |
| MRT67307 | It is a derivative of BX795 and has better selectivity for IKKε and TBK1 than for other kinases | NA | [87] |
| CYT387 | It is derived from momelotinib, JAK1/2 inhibitor that is therapeutically used to treat myelofibrosis | NA | [87] |
| K252a, dovitinib & oxindole | Similar H-bonding networks can be formed by these substances in the kinase hinge binding area which frequently showed multitarget inhibitor, TBK1 included. This compound concentrated with tozasertib, a moderately effective Aurora kinase inhibitor for TBK1. | NA | [87] |
| GSK8612 | In Ramos cells, it prevents IRF3 phosphorylation and inhibits the release of IFNβ from THP1 cell line treated by ds-DNA-containing viruses or 2C,3′-cGAMP | NA | [87] |

### 6.1 Small Molecule Inhibitor

STING, a protein involved in the Golgi network, is a possible anticancer target because of its function in phosphorylation, dimerization, and trafficking to the Golgi network. It develops a complex with TBK1, leading to IFN secretion via type-I IFNs pathway. However, none of STING inhibitors have been approved for clinical use. Several preclinical and clinical phases are investigating the effectiveness of STING inhibitors (Table 1). DITTRIN-10, DITTRIN-11, and DITTRIN-12 are dimerization inhibitors that reactivate IFN activation via the cGAS- STING pathway after electric or electro-optical stimulation administration with an mRNA vaccine [80]. CRISPR-Cas9, an effective and highly potent agonist for the induction of IFN, has been found to be effective in osteosarcoma cell line B14. More experimental studies are needed to fully understand STING's potential in cancer treatment [81]. Furthermore, Shen and his colleagues developed alendronate (Ale) based cationic platinum prodrug nanoparticles (Ale PD-NPs), which demonstrate dual-responsiveness to the osteosarcoma tumor microenvironment. Due to Ale targeting bone tissues and charge reversal effects, Ale PD-NPs exhibits a significant ability to achieve deep penetration into dense osteosarcoma tissues. Ale PD-NPs can activate immune system via the stimulation of cGAS-STING pathway, leading to the maturation of dendritic cells by utilizing platinum drugs [82]. Moreover, Zhang and his colleagues utilized a reduction sensitive polymer with pair-wised carboxyl groups, which further encapsulate with a cationic phenanthriplatin drug (PhenPt) as STING agonists to form PhenPt nanoparticles by electrostatic interactions. PhenPt NPs can release PhenPt into tumor microenvironments and subsequently induce DNA damage, and stimulate STING signaling pathway, leading to improve chemo-immunotherapeutic activity via the activation of innate and adaptive immune responses [83]. Additionally, Liu and his research team synthesized Mn-doped bioactive glass (BG-Mn) for an effective adjuvant therapy to regulate tumor metastasis and wound healing in melanoma. On one hand, $Mn^{2+}$ stimulates STING pathway to exhibit antitumor effects, on the other hand, the doping of $Mn^{2+}$ elicits excellent photothermal properties to bioactive glass that improves

the uptake of nanoparticles in cancer cells, thereby effectively demonstrating antitumor immune activation [84].

### 6.2 Gene Editing

Gene editing (GE) is the ability to delete, change, or frame a specific DNA sequence by an intended targeted mutation in a living organism. New gene editing technology from site-specific artificially defined nucleases (TALENs), zinc finger nucleases (ZFNs), and the newest technology for clustered regularly interspaced short they repeat sequences (CRISPR) has opened new research areas in life sciences, including phenotypic experiments and genetic scanning. These tools will significantly enhance the ability to decode the functions of genes, increasing the speed of mutation creation, trait optimization, and trait regeneration. Gene editing technique utilizing clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) may lessen the side effects of immune checkpoint blockade medication [89].

Although both short interfering RNA and CRISPR-Cas9 might downregulate gene editing, the CRISPR-Cas9 based knockdown approach offers the advantage of permanently silencing the target gene. Specifically, the CRISPR-Cas9 gene editing technique targets the gene sequence in sgRNA (Guide RNA), which enables Cas9 protease to effectively eliminate the target gene. Hollow manganese dioxide (HMn) is an appropriate nano-carrier for drug administration because to its large loading abilities, great response to the tumor microenvironment (TME), and minimal toxicity [90]. Further coating of HMn was done using hyaluronic acid (HA) and loaded with STING agonist MSA-2 and CRISPR-Cas9 plasmid for PD-L1 silencing. The nanoplatform was referred to as HMnO2-MSA-2-PD-L1@HA, or HMnMPH for short. The HMnPMH nanoplatform may be able to enter cancer cells through the CD44 receptor and the EPR effect. Once inside, it will breakdown and releases Mn2+, MSA-2, and Cas9/sg-PD-L1 plasmid in tumor milieu via conjunction with GSH/pH. Furthermore, MSA-2 recruits and activates IRF3 and TBK1 to start downstream signaling processes. Mn2+ can also be utilize for magnetic resonance imaging (MRI) to direct treatment. Proinflammatory cytokines including IFN-β, IL-6 as well as type I IFNs were developed, thereby stimulate STING-mediated signal transduction. The maturation and antigen presentation of dendritic cells were then facilitated by type I interferon. Additionally, by altering the PD-L1 gene, CRISPR-Cas9 triggered the development of cytotoxic T lymphocytes from immunosuppressive T cells and triggering an array of potent cellular immunological reactions that prevents tumor [91].

Several strategies can be employed to evaluate the therapeutic efficacy of gene editing in promoting STING activation. First, optimizing the design and delivery of CRISPR/Cas9 components is crucial, ensuring high specificity and efficiency in targeting genes involved in the STING pathway. This includes using advanced delivery methods such as viral vectors or lipid nanoparticles to enhance the uptake and expression of gene editing tools in target cells. Second, modulating the cellular repair pathways to favor homology-directed repair (HDR) over non-homologous end joining (NHEJ) can improve the precision of gene edits, thereby enhancing the activation of the STING pathway. Additionally, combining gene editing with other therapeutic approaches, such as immunotherapy or chemotherapy, can create a synergistic effect, boosting the overall immune response against tumors. Monitoring and evaluating the edited cells for off-target effects and ensuring the stability and functionality of the edited genes are also essential to maintain therapeutic efficacy and safety. By integrating these strategies, the potential of gene editing to enhance STING activation and improve cancer immunotherapy outcomes can be maximized [92,93].

## 7. Emerging Therapeutic Strategies

The traditional cancer treatments, e.g., chemotherapy, radiotherapy, and surgery, have been established for decades. Recently, immunotherapy against shape-tumor immunity has become a hot spot of biomedical research and clinical practice and has achieved obvious and efficient long-term therapeutic effects in some tumors. Both small molecular chemicals and biologics have been developed to selectively activate CDNs (cyclic dinucleotides) and STING through PKR purification, among which harmful STING agonists have higher potency and can induce strong and durable antitumor responses. Harmful agonists are administered through systemic, local, or vaccination delivery to attract and activate immune cells of the patient, thus achieving increased frequency and efficiency of tumor regression, preventing tumor metastasis, and enhancing durability of response. Among the most widely studied STING agonists, DMXT Dimer, which is an efficient macrofollicle delivery product, has achieved significant benefit in combination immune therapy in mice and demonstrates the positive immune response in the tumor [94].

Nowadays, the exploration of harmful agonists has extended to human beings. ADUS100 and ADUS1008, two novel agonists, have been synthesized, which can induce strong type I interferon activation both in human primary monocytes in peripheral blood and HEK293 cell lines. In particular, AGT's ALRN-6924 is currently in preclinical testing for evaluation of safety, pharmacologic, and pharmacodynamics profile suitable for intratumor injection. Additionally, the vaccines have been developed to activate antitumor immune responses, which is maximized by co-targeting STING in the cDC (conventional dendritic cell) to make DC vaccine or STING agonist vaccine. Among them, NeuVax is one preclinical STING agonist vaccine that has the Phase II Trials, which induces a 24.1% pERB2-specific cellular immune response. Immune markers that show T cell stimulation, growth of T cell and migration, additionally NK cell-mediated killing can be used to investigate the effective immune response. These markers enable successful antitumor responses in a variety of solid tumor models [63,95].

## 8. Challenges and Opportunities

The pathway known as cGAS-STING has become a critical regulator of tumor immunity, with its activation demonstrating the potential to impede initial neoplastic progression through the upregulation of ISGs and the mediation of the release of cytokines, chemokines, and proteases associated with the secretory phenotype linked to senescence, collectively restricting tumorigenesis [79]. Notably, cancer cells with Chromosome mis-segregation occurs frequently in unstable genomes during cell division, leading to the generation of micronuclei that can burst and allow the cytosol to contain the genetic contents, subsequently detected by cGAS. Moreover, the transfer of tumor-cell-derived cGAMP into immune cells can activate cGAS-STING dependent signal transduction, facilitating antigen-specific priming of T-cells. Preclinical models have further underscored the significance of cGAS-STING signaling in cancer, as evidenced by enhanced tumorigenicity and decreased CTL infiltration in tumors with lost or reduced STING expression.

While the potential of STING agonists in strengthening current immunotherapies and increasing anti-tumor immunity is well-supported, several challenges exist in the clinical targeting of the cGAS-STING pathway [96]. The administration of first-generation CDN STING agonists intratumorally limits their use to accessible tumors, prompting efforts to develop substances with enhanced systemic delivery capabilities. Concerns over the potential induction of pathologic inflammation and off-target effects on immune cells, as well as the cGAS-STING pathway's selective inactivation in some cancers, highlight the need for a comprehensive comprehension of the mechanisms causing abnormalities in STING signaling and the development of remedial procedures to boost the tumor microenvironment's response to STING agonists.

Effective delivery of STING agonists to the tumor site is challenging. Current methods, such as intratumoral injection, are limited by the accessibility of tumors and insufficient retention time in tumors [97]. Defects in immune checkpoint signaling can hinder the efficacy of STING activation. Overcoming these defects is essential for enhancing the immune response against cancer cells. The STING pathway can lead to the recruitment and activation of immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which can counteract the anti-tumor immune response. Effective antigen presentation is crucial for a robust immune response, but defects in this process can limit the efficacy of STING-based therapies [98].

## 9. Future Direction

Future directions regarding the use of STING antagonists in cancer immunotherapy were discussed. The potential of STING agonists as potent drugs for immunotherapy has been demonstrated, but there are still challenges in clinically targeting the cGAS-STING pathway. One significant barrier is the limited use of first-generation CDN STING agonists due to their requirement for intratumoral administration, which restricts them to accessible tumors. Efforts are being made to develop compounds with improved properties for systemic delivery in order to overcome this limitation [91]. However, concerns remain about the potential induction of pathologic inflammation and off-target effects on immune cells, particularly T-cells, as resulting of systemic incorporation of STING agonists. Additionally, the potential negative feedback loops and resistance mechanisms that may dampen the effect of STING agonists need further exploration.

Another area of future research is understanding the detailed understanding of the underlying molecular pathways defining sensitivity to STING agonism and identifying suitable biomarkers to determine sensitivity. This is essential for choosing the right patients to participate in clinical trials using synthetic STING agonists [82]. Furthermore, due to their susceptibility to the STING's reactivation and the signals it sends downstream, particularly STAT1, cancer types linked to the cGAS-STING pathway being deactivated, comprising KL NSCLC, possibly attractive targets of therapy for STING agonists. The cGAS-STING/TBK1 pathway represents a critical axis in innate immunity and cancer immunotherapy, offering promising avenues for future research. A primary direction involves exploring strategies to fine-tune pathway activation to enhance anti-tumor immunity while minimizing inflammatory toxicities.

## 10. Concluding Remarks

The cGAS-STING signal transduction is recognized as a significant immune regulatory mechanism for identifying cytosolic DNAs. The growing interest in cGAS-STING transduction focuses on harnessing individual patient immune system for eradicating tumors, Intriguingly, STING pathway acting as a critical immune sensor to control DNA sensing from tumors and T-cell priming. This review highlighted the crosstalk mechanism of cGAS-STING and TBK1 signaling pathway in cancer immunotherapy, which reveals a pivotal convergence of innate immunity and tumor eradication, offering profound implications for therapeutic interventions. This axis orchestrates a finely-tuned immune response by sensing cytosolic DNA through cGAS, which catalyzes cyclic GMP-AMP (cGAMP) production. Subsequently, activation of STING receptor triggers TBK1 and IRF3 signaling pathway, resulting in the production of Type-I IFNs and pro-inflammatory cytokines. This immunomodulatory cascade enhances antigen presentation, promotes dendritic cells maturation, and activates cytotoxic T-lymphocytes, facilitating robust anti-tumor immunity. Notably, cGAS-STING/TBK1 pathway demonstrated dual mechanism to foster immunogenic cell death and suppress tumor progression, an emergent therapeutic target in cancer immunotherapy to increase the therapeutic efficacy when combined with immunotherapy from cancer vaccine to ICB therapy, and CAR T-cells immunotherapy. This intricate signaling network presenting the opportunities and challenges for

the development of next generation cancer immunotherapeutic.

## Conflicts of Interest

The author declare that they have no conflicts of Interest.

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## References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a Cancer Journal for Clinicians. 2024, 74(3), 229-263. DOI: 10.3322/caac.21834

[2] Zhang SS, Xiao XY, Yi YL, Wang XY, Zhu LX, et al. Tumor initiation and early tumorigenesis: molecular mechanisms and interventional targets. Signal Transduction and Targeted Therapy. 2024, 9(1), 149. DOI: 10.1038/s41392-024-01848-7

[3] Paul P, Malakar AK, Chakraborty S. The significance of gene mutations across eight major cancer types. Mutation Research. Reviews in Mutation Research. 2019, 781, 88-99. DOI: 10.1016/j.mrrev.2019.04.004

[4] Murciano-Goroff YR, Warner AB, Wolchok JD. The future of cancer immunotherapy: microenvironment-targeting combinations. Cell Research. 2020, 30(6), 507-519. DOI: 10.1038/s41422-020-0337-2

[5] Bai RL, Chen NF, Li LY, Cui JW. A brand new era of cancer immunotherapy: breakthroughs and challenges. Chinese Medical Journal. 2021, 134(11), 1267-1275. DOI: 10.1097/CM9.0000000000001490

[6] Naser R, Dilabazian H, Bahr H, Barakat A, El-Sibai M. A guide through conventional and modern cancer treatment modalities: A specific focus on glioblastoma cancer therapy (Review). Oncology Reports. 2022, 48(5), 190. DOI: 10.3892/or.2022.8405

[7] Darvishi M, Tosan F, Nakhaei P, Manjili DA, Kharkouei SA, et al. Recent progress in cancer immunotherapy: Overview of current status and challenges. Pathology, Research and Practice. 2023, 241, 154241. DOI: 10.1016/j.prp.2022.154241

[8] Paludan SR, Pradeu T, Masters SL, Mogensen TH. Constitutive immune mechanisms: mediators of host defence and immune regulation. Nature Reviews. Immunology. 2021, 21(3), 137-150. DOI: 10.1038/s41577-020-0391-5

[9] Mukherjee AG, Wanjari UR, Namachivayam A, Murali R, Prabakaran DS, et al. Role of Immune Cells and Receptors in Cancer Treatment: An Immunotherapeutic Approach. Vaccines (Basel). 2022, 10(9), 1493. DOI: 10.3390/vaccines10091493

[10] Kim SK, Cho SW. The Evasion Mechanisms of Cancer Immunity and Drug Intervention in the Tumor Microenvironment. Frontiers in Pharmacology. 2022, 13, 868695. DOI: 10.3389/fphar.2022.868695

[11] de Visser KE, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell. 2023, 41(3), 374-403. DOI: 10.1016/j.ccell.2023.02.016

[12] Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cellular & Molecular Immunology. 2020, 17(8), 807-821. DOI: 10.1038/s41423-020-0488-6

[13] Adhikary S, Pathak S, Palani V, Acar A, Banerjee A, et al. Current Technologies and Future Perspectives in Immunotherapy towards a Clinical Oncology Approach. Biomedicines. 2024, 12(1), 217. DOI: 10.3390/biomedicines12010217

[14] Roy R, Singh SK, Misra S. Advancements in Cancer Immunotherapies. Vaccines (Basel). 2023, 11(1), 59. DOI: 10.3390/vaccines11010059

[15] Kciuk M, Yahya EB, Mohamed IMM, Rashid S, Iqbal MO, et al. Recent Advances in Molecular Mechanisms of Cancer Immunotherapy. Cancers (Basel). 2023, 15(10), 2721. DOI: 10.3390/cancers15102721

[16] Tan S, Day D, Nicholls SJ, Segelov E. Immune Checkpoint Inhibitor Therapy in Oncology: Current Uses and Future Directions: JACC: CardioOncology State-of-the-Art Review. CardioOncology. 2022, 4(5), 579-597. DOI: 10.1016/j.jaccao.2022.09.004

[17] Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nature Reviews. Immunology. 2020, 20(11), 651-668. DOI: 10.1038/s41577-020-0306-5

[18] Yu L, Liu PD. Cytosolic DNA sensing by cGAS: regulation, function, and human diseases. Signal Transduction and Targeted Therapy. 2021, 6(1), 170. DOI: 10.1038/s41392-021-00554-y

[19] Jiang ML, Chen PX, Wang L, Li W, Chen B, et al. cGAS-STING, an important pathway in cancer immunotherapy. Journal of Hematology & Oncology. 2020, 13(1), 81. DOI: 10.1186/s13045-020-00916-z

[20] Tian Z, Zeng Y, Peng Y, Liu J, Wu F. Cancer immunotherapy strategies that target the cGAS-STING pathway. Frontiers in Immunology. 2022, 13, 996663. DOI: 10.3389/fimmu.2022.996663

[21] Chen MT, Yu SB, van der Sluis T, Zwager MC, Schröder CP, et al. cGAS-STING pathway expression correlates with genomic instability and immune cell infiltration in breast cancer. NPJ Breast Cancer. 2024, 10(1), 1. DOI: 10.1038/s41523-023-00609-z

[22] Gan Y, Li XY, Han SZ, Liang Q, Ma XQ, et al. The cGAS/STING Pathway: A Novel Target for Cancer Therapy. Frontiers in Immunology. 2022, 12, 795401. DOI: 10.3389/fimmu.2021.795401

[23] Xiang S, Song SK, Tang HT, Smaill JB, Wang AQ, et al. TANK-binding kinase 1 (TBK1): An emerging therapeutic target for drug discovery. Drug Discovery Today. 2021, 26(10), 2445-2455. DOI: 10.1016/j.drudis.2021.05.016

[24] Runde AP, Mack R, S J PB, Zhang JW. The role of TBK1 in cancer pathogenesis and anticancer immunity. Journal of Experimental & Clinical Cancer Research: CR. 2022, 41(1), 135. DOI: 10.1186/s13046-022-02352-y

[25] Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. Nature Reviews. Immunology. 2021, 21(9), 548-569. DOI: 10.1038/s41577-021-00524-z

[26] Zhang Y, Zou M, Wu H, Zhu J, Jin T. The cGAS-STING pathway drives neuroinflammation and neurodegeneration via cellular and molecular mechanisms in neurodegenerative diseases. Neurobiology of Disease. 2024, 202, 106710. DOI: 10.1016/j.nbd.2024.106710

[27] Liu Y, Pu FF. Updated roles of cGAS-STING signaling in autoimmune diseases. Frontiers in Immunology. 2023, 14, 1254915. DOI: 10.3389/fimmu.2023.1254915
[28] Chen RH, Du JM, Zhu H, Ling Q. The role of cGAS-STING signalling in liver diseases. JHEP Reports: Innovation in Hepatology. 2021, 3(5), 100324. DOI: 10.1016/j.jhepr.2021.100324
[29] Hopfner KP, Hornung V. Molecular mechanisms and cellular functions of cGAS-STING signalling. Nature reviews. Molecular Cell Biology. 2020, 21(9), 501-521. DOI: 10.1038/s41580-020-0244-x
[30] Pan J, Fei CJ, Hu Y, Wu XY, Nie L, et al. Current understanding of the cGAS-STING signaling pathway: Structure, regulatory mechanisms, and related diseases. Zoological Research. 2023, 44(1), 183-218. DOI: 10.24272/j.issn.2095-8137.2022.464
[31] Zhang X, Bai XC, Chen ZJ. Structures and Mechanisms in the cGAS-STING Innate Immunity Pathway. Immunity. 2020, 53(1), 43-53. DOI: 10.1016/j.immuni.2020.05.013
[32] Pu F, Chen F, Liu J, Zhang Z, Shao Z. Immune Regulation of the cGAS-STING Signaling Pathway in the Tumor Microenvironment and Its Clinical Application. OncoTargets and Therapy. 2021, 14, 1501-1516. DOI: 10.2147/OTT.S298958
[33] Kwon J, Bakhoum SF. The Cytosolic DNA-Sensing cGAS-STING Pathway in Cancer. Cancer Discovery. 2020, 10(1), 26-39. DOI: 10.1158/2159-8290.CD-19-0761
[34] Khoo LT, Chen LY. Role of the cGAS-STING pathway in cancer development and oncotherapeutic approaches. EMBO Reports. 2018, 19(12), e46935. DOI: 10.15252/embr.201846935
[35] Pépin G, Gantier MP. cGAS-STING Activation in the Tumor Microenvironment and Its Role in Cancer Immunity. Advances in Experimental Medicine and Biology. 2017, 1024, 175-194. DOI: 10.1007/978-981-10-5987-2_8
[36] Li J, Bakhoum SF. The pleiotropic roles of cGAS-STING signaling in the tumor microenvironment. Journal of Molecular Cell Biology. 2022, 14(4), mjac019. DOI: 10.1093/jmcb/mjac019
[37] Fan XZ, Song XS, Chen WJ, Liang HT, Natatsukasa H, et al. cGAS-STING signaling in cancer: Regulation and therapeutic targeting. MedComm-Oncology Homepage. 2023, 2(3), e49. DOI: 10.1002/mog2.49
[38] Yu Y, Liu J, Liu C, Liu R, Liu L, et al. Post-Translational Modifications of cGAS-STING: A Critical Switch for Immune Regulation. Cells. 2022, 11(19), 3043. DOI: 10.3390/cells11193043
[39] Revach OY, Liu S, Jenkins RW. Targeting TANK-binding kinase 1 (TBK1) in cancer. Expert Opinion on Therapeutic Targets. 2020, 24(11), 1065–1078. DOI: 10.1080/14728222
[40] Marion JD, Roberts CF, Call RJ, Forbes JL, Nelson KT, et al. Mechanism of endogenous regulation of the type I interferon response by suppressor of IκB kinase epsilon (SIKE), a novel substrate of TANK-binding kinase 1 (TBK1). The Journal of Biological Chemistry. 2013, 288(25), 18612-23. DOI: 10.1074/jbc.M112.440859
[41] Alam M, Hasan GM, Hassan MI. A review on the role of TANK-binding kinase 1 signaling in cancer. International Journal of Biological Macromolecules. 2021, 183, 2364-2375. DOI: 10.1016/j.ijbiomac.2021.06.022
[42] Miranda A, Shirley CA, Jenkins RW. Emerging roles of TBK1 in cancer immunobiology. Trends Cancer. 2024, 10(6), 531-540. DOI: 10.1016/j.trecan.2024.02.007
[43] Wang BL, Zhang F, Wu XY, Ji M. TBK1 is paradoxical in tumor development: a focus on the pathway mediating IFN-I expression. Frontiers in Immunology. 2024, 15, 1433321. DOI: 10.3389/fimmu.2024.1433321
[44] Hu LX, Xie HB, Liu XJ, Potjewyd F, James LI, et al. TBK1 Is a Synthetic Lethal Target in Cancer with VHL Loss. Cancer Discovery. 2020, 10(3), 460-475. DOI: 10.1158/2159-8290.CD-19-0837
[45] Sun L, Wu J, Du F, Chen X, Chen ZJ. Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science. 2013, 339(6121), 786-91. DOI: 10.1126/science.1232458. Epub 2012 Dec 20
[46] Gao CQ, Chu ZZ, Zhang D, Xiao Y, Zhou XY, et al. Serine/threonine kinase TBK1 promotes cholangiocarcinoma progression via direct regulation of β-catenin. Oncogene. 2023, 42(8), 1492-1507. DOI: 10.1038/s41388-023-02651-4
[47] Samson N, Ablasser A. The cGAS-STING pathway and cancer. Nature Cancer. 2022, 3(12), 1452-1463. DOI: 10.1038/s43018-022-00468-w
[48] Lu Q, Chen Y, Li J, Zhu F, Zheng Z. Crosstalk between cGAS-STING pathway and autophagy in cancer immunity. Frontiers in Immunology. 2023, 14, 1139595. DOI: 10.3389/fimmu.2023.1139595
[49] Joshi B, Joshi JC, Mehta D. Regulation of cGAS Activity and Downstream Signaling. Cells. 2022, 11(18), 2812. DOI: 10.3390/cells11182812
[50] Hoong BYD, Gan YH, Liu H, Chen ES. cGAS-STING pathway in oncogenesis and cancer therapeutics. Oncotarget. 2020, 11(30), 2930-2955. DOI: 10.18632/oncotarget.27673
[51] Li X, Shu C, Yi GH, Chaton CT, Shelton CL, et al. Cyclic GMP-AMP synthase is activated by double-stranded DNA-induced oligomerization. Immunity. 2013, 39(6), 1019-31. DOI: 10.1016/j.immuni.2013.10.019
[52] Bai JL, Liu F. The cGAS-cGAMP-STING Pathway: A Molecular Link Between Immunity and Metabolism. Diabetes. 2019, 68(6), 1099-1108. DOI: 10.2337/dbi18-0052
[53] Marcus A, Mao AJ, Lensink-Vasan M, Wang L, Vance RE, et al. Tumor-Derived cGAMP Triggers a STING-Mediated Interferon Response in Non-tumor Cells to Activate the NK Cell Response. Immunity. 2018, 49(4), 754-763.e4. DOI: 10.1016/j.immuni.2018.09.016
[54] Yu XY, Zhao Z, Jiang ZF. Recent progress on the activation of the cGAS-STING pathway and its regulation by biomolecular condensation. Journal of Molecular Cell Biology. 2022, 14(6), mjac042. DOI: 10.1093/jmcb/mjac042
[55] Wang ZL, Chen N, Li ZY, Xu G, Zhan XY, et al. The Cytosolic DNA-Sensing cGAS-STING Pathway in Liver Diseases. Frontiers in Cell and Developmental Biology. 2021, 9, 717610. DOI: 10.3389/fcell.2021.717610
[56] Mukai K, Konno H, Akiba T, Uemura T, Waguri S, et al. Activation of STING requires palmitoylation at the Golgi. Nature Communications. 2016, 7, 11932. DOI: 10.1038/ncomms11932
[57] Xu Q, Xing J, Wang SJ, Peng HY, Liu YZ. The role of the cGAS-STING pathway in metabolic diseases. Heliyon. 2024, 10(12), e33093. DOI: 10.1016/j.heliyon.2024.e33093
[58] Hussain B, Xie YF, Jabeen U, Lu DF, Yang B, et al. Activation of STING Based on Its Structural Features. Frontiers in Immunology. 2022, 13, 808607. DOI: 10.3389/fimmu.2022.808607
[59] Zhang LL, Wei XB, Wang ZM, Liu PY, Hou YF, et al. NF-κB activation enhances STING signaling by altering microtubule-mediated STING trafficking. Cell Reports. 2023, 42(3), 112185. DOI: 10.1016/j.celrep.2023.112185
[60] Du HS, Xu TM, Cui MH. cGAS-STING signaling in cancer immunity and immunotherapy. Biomedicine & Pharmacotherapy. 2021, 133, 110972. DOI: 10.1016/j.biopha.2020.110972

[61] Vashi N, Bakhoum SF. The Evolution of STING Signaling and Its Involvement in Cancer. Trends in Biochemical Sciences. 2021, 46(6), 446-460. DOI: 10.1016/j.tibs.2020.12.010

[62] Wang Y, Luo JW, Alu A, Han XJ, Wei YQ, et al. cGAS-STING pathway in cancer biotherapy. Molecular Cancer. 2020, 19(1), 136. DOI: 10.1186/s12943-020-01247-w

[63] Zhang JW, Yu SH, Peng Q, Wang P, Fang L. Emerging mechanisms and implications of cGAS-STING signaling in cancer immunotherapy strategies. Cancer Biology & Medicine. 2024, 21(1), 45-64. DOI: 10.20892/j.issn.2095-3941.2023.0440

[64] Saeed AFUH, Ruan XL, Guan HX, Su JQ, Ouyang SY. Regulation of cGAS-Mediated Immune Responses and Immunotherapy. Advanced Science. 2020, 7(6), 1902599. DOI: 10.1002/advs.201902599

[65] Zheng JY, Mo JL, Zhu T, Zhuo W, Yi YN, et al. Comprehensive elaboration of the cGAS-STING signaling axis in cancer development and immunotherapy. Molecular Cancer. 2020, 19(1), 133. DOI: 10.1186/s12943-020-01250-1

[66] Su T, Zhang Y, Valerie K, Wang XY, Lin SB, et al. STING activation in cancer immunotherapy. Theranostics. 2019, 9(25), 7759-7771. DOI: 10.7150/thno.37574

[67] Kumar V, Bauer C, Stewart IV JH. Cancer cell-specific cGAS/STING Signaling pathway in the era of advancing cancer cell biology. European Journal of Cell Biology. 2023, 102(3), 151338. DOI: 10.1016/j.ejcb.2023.151338

[68] Pulendran B, S. Arunachalam P, O'Hagan, DT. Emerging concepts in the science of vaccine adjuvants. Nature Reviews. Drug Discovery. 2021, 20(6), 454-475. DOI: 10.1038/s41573-021-00163-y

[69] Kim YJ. STINGing the Tumor's immune evasion mechanism. Oncoimmunology. 2018, 7(4), e1083673. DOI: 10.1080/2162402X.2015.1083673

[70] Fu J, Kanne DB, Leong M, Glickman LH, McWhirter SM, et al. STING agonist formulated cancer vaccines can cure established tumors resistant to PD-1 blockade. Science Translational Medicine. 2015, 7(283), 283ra52. DOI: 10.1126/scitranslmed.aaa4306

[71] Li AP, Yi M, Qin S, Song YP, Chu Q, et al. Activating cGAS-STING pathway for the optimal effect of cancer immunotherapy. Journal of Hematology & Oncology. 2019, 12(1), 35. DOI: 10.1186/s13045-019-0721-x

[72] Miao L, Li LX, Huang YX, Delcassian D, Chahal J, et al. Delivery of mRNA vaccines with heterocyclic lipids increases anti-tumor efficacy by STING-mediated immune cell activation. Nature Biotechnology. 2019, 37(10), 1174-1185. DOI: 10.1038/s41587-019-0247-3

[73] Hines JB, Kacew AJ, Sweis RF. The Development of STING Agonists and Emerging Results as a Cancer Immunotherapy. Current Oncology Reports. 2023, 25(3), 189-199. DOI: 10.1007/s11912-023-01361-0

[74] Huang CQ, Shao N, Huang YY, Chen JF, Wang D, et al. Overcoming challenges in the delivery of STING agonists for cancer immunotherapy: A comprehensive review of strategies and future perspectives. Materials Today. Bio. 2023, 23, 100839. DOI: 10.1016/j.mtbio.2023.100839

[75] Harding SM, Benci JL, Irianto J, Discher DE, Minn AJ, et al. Mitotic progression following DNA damage enables pattern recognition within micronuclei. Nature. 2017, 548(7668), 466-470. DOI: 10.1038/nature23470

[76] Ager CR, Reilley MJ, Nicholas C, Bartkowiak T, Jaiswal AR, et al. Intratumoral STING Activation with T-cell Checkpoint Modulation Generates Systemic Antitumor Immunity. Cancer Immunology Research. 2017, 5(8), 676-684. DOI: 10.1158/2326-6066.CIR-17-0049

[77] Hu YW, Zhang J, Wu XM, Cao L, Nie P, et al. TANK-Binding Kinase 1 (TBK1) Isoforms Negatively Regulate Type I Interferon Induction by Inhibiting TBK1-IRF3 Interaction and IRF3 Phosphorylation. Frontiers in Immunology. 2018, 9, 84. DOI: 10.3389/fimmu.2018.00084

[78] Sun Y, Revach OY, Anderson S, Kessler EA, Wolfe CH, et al. Targeting TBK1 to overcome resistance to cancer immunotherapy. Nature. 2023, 615(7950), 158-167. DOI: 10.1038/s41586-023-05704-6

[79] Motedayen Aval L, Pease JE, Sharma R, Pinato DJ. Challenges and Opportunities in the Clinical Development of STING Agonists for Cancer Immunotherapy. Journal of Clinical Medicine. 2020, 9(10), 3323. DOI: 10.3390/jcm9103323

[80] Kemmoku H, Kuchitsu Y, Mukai K, Taguchi T. Specific association of TBK1 with the trans-Golgi network following STING stimulation. Cell Structure and Function. 2022, 47(1), 19-30. DOI: 10.1247/csf.21080

[81] Chen C, Xu P. Cellular functions of cGAS-STING signaling. Trends in Cell Biology. 2023, 33(8), 630-648. DOI: 10.1016/j.tcb.2022.11.001

[82] Shen MF, Wang YS, Bing TJ, Tang YJ, Liu XY, et al. Alendronate Triggered Dual-Cascade Targeting Prodrug Nanoparticles for Enhanced Tumor Penetration and STING Activation of Osteosarcoma. Advanced Functional Materials. 2023, 33(49), 2307013. DOI: 10.1002/adfm.202307013

[83] Zhang L, Shang K, Li X, Shen M, Lu S, et al. Reduction Sensitive Polymers Delivering Cationic Platinum Drugs as STING Agonists for Enhanced Chemo-Immunotherapy. Advanced Functional Materials. 2022, 32(43), 2204589. DOI: 10.1002/adfm.202204589

[84] Liu XY, Shen MF, Bing TJ, Zhang XY, Li YF, et al. A Bioactive Injectable Hydrogel Regulates Tumor Metastasis and Wound Healing for Melanoma via NIR-Light Triggered Hyperthermia. Advanced Science. 2024, 11(26), e2402208. DOI: 10.1002/advs.202402208

[85] Liu KF, Lan YQ, Li XL, Li MY, Cui L, et al. Development of small molecule inhibitors/agonists targeting STING for disease. Biomedicine & Pharmacotherapy. 2020, 132, 110945. DOI: 10.1016/j.biopha.2020.110945

[86] Guerini D. STING Agonists/Antagonists: Their Potential as Therapeutics and Future Developments. Cells. 2022, 11(7), 1159. DOI: 10.3390/cells11071159

[87] Ding CY, Song ZL, Shen AC, Chen TT, Zhang A. Small molecules targeting the innate immune cGAS-STING-TBK1 signaling pathway. Acta Pharmaceutica Sinica B. 2020, 10(12), 2272-2298. DOI: 10.1016/j.apsb.2020.03.001

[88] Sasaki N, Homme M, Kitajima S. Targeting the loss of cGAS/STING signaling in cancer. Cancer Science. 2023, 114(10), 3806-3815. DOI: 10.1111/cas.15913

[89] Kato-Inui T, Takahashi G, Hsu S, Miyaoka Y. Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 with improved proof-reading enhances homology-directed repair. Nucleic Acids Research. 2018, 46(9), 4677-4688. DOI: 10.1093/nar/gky264

[90] Gao FY, Wu YY, Wang RT, Yao YH, Liu YQ, et al. Precise nano-system-based drug delivery and synergistic therapy against androgen receptor-positive triple-negative breast cancer. Acta Pharmaceutica Sinica. B. 2024, 14(6), 2685-2697. DOI: 10.1016/j.apsb.2024.03.012

[91] Lu QL, Chen RY, Du SY, Chen C, Pan YC, et al. Activation of the cGAS-STING pathway combined with CRISPR-Cas9 gene editing triggering long-term immunotherapy. Biomaterials. 2022, 291, 121871. DOI: 10.1016/j.biomaterials.2022.121871

[92] Wiles MV, Qin WN, Cheng AW, Wang HY. CRISPR-Cas9-mediated genome editing and guide RNA design.

Mammalian Genome. 2015, 26(9-10), 501-10. DOI: 10.1007/s00335-015-9565-z

[93] Li Y, Zhu ZR, Hua SY, Wan YH, Chen Q, et al. Metal-based nanoparticles promote the activation of cGAS-STING pathway for enhanced cancer immunotherapy. Nano Today. 2024, 58, 102445. DOI: 10.1016/j.nantod.2024.102445

[94] Herhaus L. TBK1 (TANK-binding kinase 1)-mediated regulation of autophagy in health and disease. Matrix Biology. 2021, 100-101, 84-98. DOI: 10.1016/j.matbio.2021.01.004

[95] Chen X, Xu ZJ, Li TF, Thakur A, Wen Y, et al. Nanomaterial-encapsulated STING agonists for immune modulation in cancer therapy. Biomarker Research. 2024, 12(1), 2. DOI: 10.1186/s40364-023-00551-z

[96] Amouzegar A, Chelvanambi M, Filderman JN, Storkus WJ, Luke JJ. STING Agonists as Cancer Therapeutics. Cancers (Basel). 2021, 13(11), 2695. DOI: 10.3390/cancers13112695

[97] Wu YT, Fang Y, Wei Q, Shi H, Tan HL, et al. Tumor-targeted delivery of a STING agonist improves cancer immunotherapy. Proceedings of the National Academy of Sciences. 2022, 119(49), e2214278119. DOI: 10.1073/pnas.2214278119

[98] Xu Y, Xiong Y. Targeting STING signaling for the optimal cancer immunotherapy. Frontiers in Immunology. 2024, 15, 1482738. DOI: 10.3389/fimmu.2024.1482738