Proceedings of the 6th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/2026.38717

# *Targeting cGAS-STING: From Genomic Instability to Cancer Immunity*

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***Abstract.*** Genomic instability is a hallmark of cancer, which promotes the occurrence, progression, and resistance to treatment of cancer by promoting the accumulation of genetic and epigenetic changes. In addition to promoting malignant transformation, genomic instability can also lead to abnormally localized DNA species, such as micronucleus DNA, chromosome fragments, and extrachromosomal DNA, which are recognized by the interferon gene promoter (STING) pathway. This pathway is regulated by cyclic GMP-AMP synthase (cGAS), which is the key axis of innate immune surveillance. The activation of the cGAS-STING pathway then triggers downstream transcriptional cascades, including the IRF3 signaling pathway and the NF-κB signaling pathway, which in turn up-regulates the expression of type I interferons, pro-inflammatory cytokines, and chemokines, and ultimately promotes anti-tumor immune responses. However, more and more evidence shows that the cGAS-STING pathway has a significant dual role in cancer progression, which means that cGAS-STING is intertwined with complex nonlinear networks in different cell types and different stages of cancer development. Therefore, elucidating the spatiotemporal regulation mechanism of the cGAS-STING axis and its downstream effectors in different stages of tumorigenesis, malignant progression, metastasis and diffusion has become a key research priority. Based on the above considerations, this paper reviews the existing knowledge about the interaction between the cGAS-STING axis and genomic instability and cancer immunity, especially focusing on the mechanism basis of its abnormal regulation, potential therapeutic value, and the urgent need to adopt precise guidance strategies to identify individuals most likely to benefit from treatment for this pathway.

***Keywords:*** Genomic Instability, cGAS-STING, Cancer, Cancer Immunity

## 1. Introduction

Gene instability is the main feature of cancer cells, which can lead to continuous genetic and epigenetic changes. These changes constitute the basis of cancer occurrence, progression, metastasis and treatment of drug resistance [1, 2]. By increasing the mutation rate, genomic instability accelerates the acquisition of various cancer markers, including continuous proliferation signal transduction and immune escape, thus becoming the main driving force for malignant evolution [1]. A key feature of this process is, out of context, DNA production - that is, DNA fragments break

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DOI: 10.54254/2753-8818/2026.38717

through their normal localization regions. Micronucleus breakdown, replication fork collapse, and mitochondrial dysfunction together lead to the release of DNA into the cytoplasm, which is recognized as a danger signal, rather than its own DNA [3, 4]. However, this instability itself exposes cancer cells to unique therapeutic weaknesses: they are highly dependent on specific DNA repair pathways, such as ATR-CHK1 and homologous recombination, which provide the possibility for synthetic lethality. This principle has been verified by DDR inhibitors in cancer, which has promoted the development of precision oncology, making genomic instability no longer just a disease driver [2, 5]. In addition to its dependence on DNA repair, genomic instability also triggers a unique susceptibility: the abnormal DNA species it produces can act as powerful activators of the cGAS-STING innate immune surveillance axis, which functions like a cellular alarm system and can recruit and activate anti-cancer immune responses [3, 6, 7]. One of the most important mechanisms of immune surveillance is the cGAS-STING axis, which senses DNA in the cytoplasm and coordinates anti-cancer immunity - when the system functions, it can be cleared before cancer cells have colonized [6, 7].

The cGAS-STING axis constitutes a DNA monitoring system for detecting cytoplasmic DNA. As a key innate immune sensor, cGAS can recognize foreign nucleic acids from bacteria, viruses and other extracellular sources, thereby activating STING, initiating downstream transcription of IFN and inflammatory cytokines, and ultimately triggering an immune response against pathogens [6, 8, 9]. In the context of cancer, it is the instability of the cancer genome that triggers the activation of this pathway [3, 4]. Under physiological conditions, the activation of the cGAS-STING axis can promote the transcription of pro-inflammatory cytokines, chemokines and other downstream immune effector molecules, thereby inducing apoptosis and activating innate immunity. These coordinated responses help to eliminate cells that carry genomic instability, which in turn serves as an important barrier against malignant transformation [3, 6].

However, more and more evidence shows that the cGAS-STING signaling pathway is not a one-way role in cancer progression, which requires further study. In this context, this paper reviews the role of cGAS-STING axis in cancer immunity, aiming to clarify the functional correlation of cGAS-STING in the whole process of cancer initiation and progression, promote a deeper understanding, and provide new ideas for the future development of anti-cancer treatment and preventive drugs targeting cGAS-STING axis.

## 2. Genomic instability in cancer

### 2.1. DNA repair defects

In tissue cells, DNA damage response system includes DNA damage signal transduction and a variety of DNA repair strategies. With the complex network of signal transduction and repair, cells can efficiently remove DNA damage from external damage and internal genomic disturbance, thus effectively maintaining genomic stability [2, 10, 11]. However, in cancer cells, DNA repair defects are a fundamental mechanism leading to genomic instability. Cancer cells often have defects in multiple DNA damage repair and response pathways, which in turn weakens genomic integrity. In the context of cancer, the main DNA damage repair disorder is the disorder of HR (homologous recombination). Abnormalities in core proteins such as BRCA1, BRCA2, PALB2, and RAD51 involved in HR disorders in cancer can disrupt the accurate repair of DNA double-strand breaks and replication-related damage [12]. In addition, in addition to the impaired HR repair mechanism in cancer cells, the dysfunction of mismatch repair (MMR) system further weakens the template-dependent efficient and accurate repair ability in cancer cells. Mismatch repair mainly depends on

DOI: 10.54254/2753-8818/2026.38717

MLH1, MSH2, MSH6 and PMS2, and the abnormal expression or loss of mutant function of these proteins leads to the accumulation of errors in the process of DNA replication, which leads to microsatellite instability [13, 14]. When HR repair cannot be performed, non-homologous end joining (NHEJ) defects - another major DNA double-strand break repair mechanism - will further reduce the ability of cells to effectively sense DNA damage and initiate checkpoint signaling pathways involving ATM and ATR, exacerbating the accumulation of DNA damage [2, 15]. In addition to HR, nucleotide excision repair and base excision repair defects contribute to different mutation characteristics [10, 16].

If the unrepaired single-strand break (SSB) persists until the replication fork encounters them, it may be converted into double-strand break (DSB), which is the main source of genomic instability in cancer cells with defective double-strand break repair mechanisms [17]. These repair defects not only allow the accumulation of mutations, but also actively shape the mutant landscape that determines the evolution of cancer. When the SSB repair is impaired, the damage is retained throughout the cell cycle due to the lack of a more accurate inspection mechanism, resulting in an abnormal response during the replication fork [18, 19]. Further, the abnormal response will cause the forward movement of the replication fork to be blocked, causing fork stagnation, fork collapse, and turning the existing SSB into a single-ended DSB. Therefore, the accumulation of DNA damage associated with replication may exceed the ability of alternative repair pathways, leading to persistent DSB, abnormal DNA repair, chromosome rearrangement, and genomic instability. It is worth noting that SSB and its subsequent DSB together lead to abnormal DNA repair and aggregation to form genomic instability. This unstable characteristic will subsequently significantly generate abnormal DNA structure, which in turn generates DNA nuclei ectopically into the cytoplasm. Abnormal DNA entering the cytoplasm ultimately activates the cGAS-STING pathway [3, 4, 20].

## 2.2. Chromosomal instability

Chromosome instability (CIN) is a typical manifestation of genomic instability, which is characterized by continuous changes in the number and structure of chromosomes during cell division. CIN is a common feature in a variety of cancer cells (including lung cancer, leukemia, etc.). CIN occurs in 60 % to 80 % of human cancers and can promote metastasis, treatment resistance, and immune escape [21-24]. Replication stress, DNA damage, cell cycle checkpoint dysfunction, and chromosome separation errors can all lead to CIN.At the same time, the above mechanisms are not independent and often cross-linked to form a network of mechanisms. Persistent replication stress can lead to replication fork stagnation and collapse, which in turn leads to double-strand breaks and chromosome fragments; abnormal centriole function, spindle assembly, kinetochore-microtubule junction or mitotic checkpoint defects can lead to chromosome mismatch and aneuploidy [25]. Chromosomal mismatches and aneuploidy changes remain to some extent during mitosis, allowing this genomic instability at the chromosomal level to be preserved from the mother cell to the daughter cell generation [26, 27].

In addition to changes in chromosome copy number, CIN can also lead to a series of abnormal chromosome structures related to cGAS perception, such as lagging chromosomes, deletion arm fragments, chromatin bridges, and micronucleus [28, 29]. Micronuclei are formed when chromosomes or chromosome fragments are not wrapped in the primary nucleus when they are mistakenly separated. They act as a key interface between genomic instability and cytoplasmic DNA perception. Micronucleus is initially produced with a relatively defective membrane structure, accompanied by abnormal nuclear pore transfer, making micronuclei easily enter the cytoplasm

DOI: 10.54254/2753-8818/2026.38717

outside the nucleus and rupture [3]. Once broken, the DNA and histones contained therein are exposed to the cytoplasm, thereby providing an endogenous source of cytoplasmic DNA that can be detected by the innate immune sensor. In addition, CIN also promotes the accumulation of chromosome fragments in the cytoplasm through chromosome breakage, abnormal DNA replication, and chromosome segregation defects, while overt dominant DNA (ecDNA) from amplified genomic regions and chromosome rearrangements constitutes another important manifestation of genomic instability [30, 31]. CIN combined with its subsequent cytoplasmic DNA exposure and ecDNA transformed the characteristic phenomenon of nuclear genome instability into a DNA space signal exposed in the cytoplasm. The spatial signal of ectopic DNA further initiates the cGAS-STING pathway, and thus CIN becomes a key bridge linking the tumor genome to the activation of the cGAS-STING pathway.

### 2.3. Therapy-induced genomic instability

Cancer therapy itself may be contradictory, inducing genomic instability in cancer cells and normal tissues, thereby establishing an additional link between DNA damage and cGAS-STING activation [32, 33]. Traditional anticancer therapies, such as radiotherapy and chemotherapy drugs that cause DNA damage, exert cytotoxic effects by causing DNA damage (including single-strand breaks, double-strand breaks, DNA cross-linking, and replication-related damage) [32, 33]. Although these injuries are designed to clear cancer cells, surviving cells that are incompletely or incorrectly repaired can lead to persistent genomic abnormalities. In particular, the error-prone repair of double-strand breaks, the continuous genotoxic pressure leading to the collapse of the replication fork, and the subsequent chromosome separation errors during cell division may produce chromosome fragments, rearrangements, micronucleus and other chromosome instability phenotypes [34]. Therefore, treatment-induced DNA damage may persist after initial damage formation and develop into persistent genomic instability in surviving cancer cells [35, 36]. Once DNA damage exceeds the cell 's ability to repair, or the cell re-enters the cell cycle when the damage has not been completely repaired, the damaged chromosome may be wrongly repaired or misseparated, resulting in acentric chromosome fragments, lagging chromosomes, chromatin bridges, and micronucleus [37]. Therefore, on the one hand, cancer treatment interventions can also lead to the instability of the cancer cell genome. At the same time, it can also produce nuclear DNA heterolocation in the cytoplasm through chromosome damage, and subsequently cause cGAS recognition activation [38].

## 3. cGAS-STING signaling pathway

The cyclic guanosine monophosphate-adenylate synthase (cGAS) -interferon gene stimulator (STING) pathway is a core component of innate immunity. The function of cGAS-STING is to link the recognition of abnormal DNA in the cytoplasm to inflammation and antiviral responses [39-41]. STING, also known as TMEM173, ERIS or MPYS, was initially identified as a key mediator of cytoplasmic DNA-induced type I interferon response. Subsequently, it was found that STING is a membrane-anchored signal protein that can detect cyclic dinucleotides [42-44]. In 2013, a key progress was made: several research teams independently reported that cytoplasmic DNA could induce the production of cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), which acts as a second messenger to activate STING. At the same time, they also identified the previously uncharacterized enzyme cGAS for the first time, which is a cytoplasmic DNA sensor responsible for the synthesis of cGAMP [8, 9]. Wu et al.confirmed that DNA stimulation can induce the production of cGAMP, and the binding of cGAMP to STING can drive the activation of IRF3

DOI: 10.54254/2753-8818/2026.38717

and promote the expression of type I interferon. Sun et al.identified that cGAS is a DNA-dependent enzyme that catalyzes the synthesis of cGAMP. Further structural and biochemical studies of cGAS elucidate the molecular mechanism of cGAS activation by binding to DNA, and reveal the unique 2 ' -5 ' phosphodiester bond in cGAMP. The 2 ' -5 ' phosphodiester bond structure of cGAMP can effectively activate STING in the cytoplasm and cause downstream related reactions. These findings together establish the cGAS-STING pathway as the basic molecular mechanism for cells to convert abnormal DNA in the cytoplasm into innate immune signals.

In normal non-cancer cells, DNA is located in the nucleusand mitochondria, effectively separated from the cytoplasm. However, genomic instability in cancer cells disrupts this separation, causing DNA fragments to be released into the cytoplasm and recognized as danger signals. cGAS is a double-stranded DNA sensor with a highly conserved catalytic domain and two different DNA binding sites. When cGAS binds to double-stranded DNA in the cytoplasm, its conformational changes are manifested as: cGAS forms an oligomeric complex with dsDNA at a stoichiometric ratio of 2: 2, and the conserved ' activation ring ' located near the DNA binding surface undergoes a switch-like conformational change, thereby relieving the self-inhibition state and making the catalytic pocket accessible and catalytic. The activated cGAS catalyzes the formation of an atypical cyclic dinucleotide using ATP and GTP as substrates. The cGAMP catalyzed by cGAS acts as a second messenger, which diffuses into the endoplasmic reticulum and binds to the pocket formed by the ligand binding domain of the cytoplasmic side of the STING dimer. After binding to the ligand, the ligand binding domain of STING rotates about 180 ° relative to the transmembrane domain, changing from an open conformation to a closed conformation, and then forming high-order oligomers by side stacking, providing a platform for the recruitment and activation of downstream TBK1. TBK1 is phosphorylated by interferon regulatory factor 3 (IRF3) after recruitment and activation by STING. Phosphorylated IRF3 dimerizes, then enters the nucleus and initiates type I interferon transcription [45-48].

At the same time, STING mediates the activation of NF-κB pathway through IKK kinase, thereby inducing the expression of pro-inflammatory cytokines such as TNF, IL-1 and IL-6. These coordinated transcription programs work together to form an antiviral and anticancer state. In addition to this classical pathway, the non-classical activation pathway of STING can also function independently of cGAS [6, 49]. After etoposide-induced DNA damage, IFI16, ATM and PARP-1 promote the assembly of an alternative STING signaling complex composed of IFI16, p53 and TRAF6. In this complex, TRAF6 catalyzes the ubiquitination of STING, thereby activating NF-κB and initiating a gene expression program different from that induced by the classical pathway. Essentially, the same genomic instability that causes malignant transformation also activates the immune system, which explains why not all cells carrying the mutation develop cancer [50, 51]. When the pathway operates normally, it can clear genomically unstable cells before cancer cell formation.

After STING is activated, the anti-cancer response is not a single path, but several lines bite each other and jointly remove genomically unstable cells. At the cellular level: STING signal can induce cell senescence, which is equivalent to pressing the damaged cells in place before they are really transformed and not allowing them to continue to proliferate. Immune priming: STING activation can drive dendritic cells (DCs), which capture DNA from tumors under the action of type I interferon signals, and then present antigens to CD8 T cells. At the same time, STING signaling also maintains the stem cell-like characteristics of CD8 T cells through the transcription factor TCF1, and promotes the differentiation of CD4 T cells into Th1 and Th9 subsets; these two subsets secrete IFN-γ and IL-9, respectively, pushing the anti-tumor immune function further up [52]. STING activation

DOI: 10.54254/2753-8818/2026.38717

recruits natural killer cells (NK cells) through chemokines such as CXCL9 and CXCL10, and promotes the expression of NKG2D ligands, such as RAE1, on the surface of cancer cells, making the cytotoxicity of NK cells easier to play. The microenvironment level is also rewritten: STING activation reduces immunosuppressive myeloid-derived suppressor cells (MDSCs) and promotes the formation of an inflammatory microenvironment, making it easier for immune cells to infiltrate [53]. These sets of mechanisms are not separate, but interrelated and synergistic - transforming the cytoplasmic DNA produced by genomic instability into a coordinated immune response that is ultimately used to identify and eliminate emerging cancer cells.

## 4. Cancer immune evasion through cGAS-STING dysregulation

Although it has the function of inhibiting cancer cells, cancer cells can still evade the immune cGAS-STING pathway through two different mechanisms: one is to reduce the availability of cGAMP to prevent its activation, and the other is to overactivate the pathway and use chronic inflammation to promote cancer cell growth and metastasis [54].

The first escape strategy is to reduce the concentration of cGAMP, thereby preventing the activation of STING. Cancer cells achieve this goal in a number of ways. The hydrolysis of extracellular cGAMP is catalyzed by exogenous nucleotide diphosphatase / phosphodiesterase 1 (ENPP1), which is often overexpressed on the surface of cancer cells and is degraded before STING is activated in immune cells [55]. In addition, many cancers silence cGAS or STING in an epigenetic manner through hypermethylation of the promoter, thereby effectively blocking the pathway at the source. In cancer, especially after radiotherapy, the cytoplasmic DNA degrading enzyme TREX1 is often up-regulated, which degrades DNA before cGAS is detected, thereby limiting the immunogenicity of DNA damage therapy [38]. In addition, cancer cells can expel cGAMP from the cell through the ABCC1 transporter, reducing the level of cGAMP in the cell and preventing its own activation [56, 57]. At the same time, the extracellular cGAMP was hydrolyzed by ENPP1, which inhibited the activation of cGAS-STING both inside and outside the cancer cells.

The second strategy is that cancer can promote its growth by over-activating the cGAS-STING signaling pathway. Although controlled STING activation has a tumor suppressor effect, chronic or excessive activation will shift the output of this pathway from protective immunity to pro-cancer inflammatory response [58, 59]. In chromosomally unstable cancers, non-canonical NF-κB is pulled up by the continuous STING signal. This pathway will lead to the production of IL-6, and then the STAT3 signal is activated, and the survival and metastasis of cancer cells will be pushed [60]. Persistent, low-level STING activation does not act as an acute signal, but drags out a chronic inflammation. This inflammation disrupts calcium homeostasis, and the protein folding environment of the endoplasmic reticulum deteriorates. Chronic endoplasmic reticulum stress eventually forces T cells to apoptosis. B cells go the other way: STING induces IL-35 secretion by IRF3 (independent of type I interferon), and IL-35 then suppresses the proliferation and anti-tumor function of NK cells. In the case of brain metastasis, cancer-derived cGAMP is transmitted to astrocytes through gap junctions, and the activation of STING in these cells promotes the production of cytokines, thereby promoting metastatic growth [58, 59]. In this case, the cGAS-STING signal not only failed to achieve the killing effect on cancer cells, but also promoted the occurrence, progression and metastasis of cancer due to the increased levels of inflammatory factors such as IL6.

DOI: 10.54254/2753-8818/2026.38717

## 5. Exploiting cGAS-STING for cancer immunotherapy

cGAS-STING may be helpful or confusing in cancer, so the treatment cannot be one-size-fits-all, depending on the specific case. The current path is roughly two types: either activate it or regulate it. The most direct way is to give STING agonists - these drugs do not rely on cGAMP, they can bind to STING and activate it. Representative drugs include natural cyclic dinucleotides (CDNs), as well as synthetic CDN compounds such as ADU-S100 and MK-1454. In preclinical studies, these compounds can indeed induce a strong anti-cancer immune response, and T cell memory is maintained for a long time [61]. In the phase I trial, ADU-S100 was only partially effective in 47 patients, while MK-1454 alone did not show activity [62]. There are more than one reason-short half-life, limited systemic immune activation, and large doses that kill T cells and dendritic cells. In addition, cGAS or STING genes are epigenetically silenced in many human cancers, such tumors do not respond to STING agonists.

Another idea is to hold down the negative regulators that help cancer escape immunity. ENPP1 inhibitors can block the degradation of extracellular cGAMP, so the endogenous danger signal becomes stronger, and the anti-cancer immune response also follows [63]. TREX1 inhibitors prevent cytoplasmic DNA from being degraded, allowing cGAS to have more ligands to perceive [38]. Epigenetic modifiers (such as DNA methyltransferase inhibitors) go the other way: in some cancer cells, the promoters of cGAS and STING are silenced by hypermethylation, and these drugs can pull their expression back. There are also ways to block CD47 or TIM3. CD47 blocking is biased towards allowing DCs to retain DNA from degradation after engulfing tumor cells, and TIM-3 blocking is biased towards allowing cDC1 to take more DNA from the outside of the cell. The two pathways eventually converge to cGAS-STING, but the entry and intracellular processing methods are different [64]. Ultimately, these strategies are restoring the ability of this pathway to detect and respond to genomic instability. In addition to monotherapy, a reasonable combination is critical: STING agonists are paired with immune checkpoint inhibitors, DNA damage therapy (radiotherapy, PARP inhibitors), CAR-T cell therapy, and demethylating agents to help re-activate pathway activity in silenced cancer cells.

However, precision remains the greatest challenge. STING is expressed on almost any cell, and systemic administration of agonists, cytokine storms, and autoimmune reactions are easy to follow. Now there are several ways to try to improve the selectivity of cancer cells: nanoparticle delivery systems, antibody-STING agonist conjugates, and STING proton channel blocker C53-the latter wants to do is to separate the beneficial IRF3-IFN signal from the harmful inflammatory response.

On the other hand, STING antagonists may be beneficial in cancer with high chromosomal instability - chronic STING activation promotes IL-6-STAT3-mediated metastasis [65]. Therefore, the goal is not just to activate or inhibit cGAS-STING, but to find the balance: acute protective immunity should be enhanced, and chronic cancer-promoting inflammation should be avoided. Looking further ahead, precision therapy is the way to target cGAS-STING-picking out tumor patients with complete signaling pathways and immunologically cold type, and developing a new generation of agonists with higher bioavailability and lower toxicity.

## 6. Discussion

At the intersection of genomic instability and cancer immunity, the role of the cGAS-STING pathway is somewhat two-sided: it acts as a barrier to carcinogenesis and, under certain conditions, pushes cancer cells forward [6, 7, 66]. The old line of genomic instability is the accumulation of mutations, the accumulation of chromosomal changes, and the promotion of malignant

DOI: 10.54254/2753-8818/2026.38717

transformation; however, the same process will also produce DNA fragments with wrong positions, which are exactly the substrates that cGAS can perceive. In other words, the genomic instability that drives carcinogenesis, in turn, may signal an endogenous danger, setting the immune surveillance on fire. When the pathway is normal and moderately activated, it promotes the identification and clearance of genomically unstable cells by several sets of methods: cancer cell self-aging response, dendritic cell activation, T cell activation, NK cell recruitment, and remodeling of the cancer microenvironment. However, cancer cells are not standing to be beaten. They can bypass monitoring at several levels-TREX1 degrades cytoplasmic DNA, epigenetic silencing cGAS or STING, ENPP1 degrades cGAMP extracellularly, and then cGAMP is discharged extracellularly by ABCC1. Conversely, if this pathway is chronic or abnormally activated, inflammatory signals will not stop, and in some cancer situations it may help tumor growth, immune adaptation and metastasis.

Important implications for cancer therapy arise from the context-dependent and dual functions of cGAS-STING signaling. Therapeutic STING activation, agonists such as ADU-S100 and MK-1454 have provided important conceptual verification [62]. However, clinical transformation is still stuck on several hurdles: pharmacokinetic characteristics, tumor-targeted delivery, pathway specificity, tumor heterogeneity, and the risk of excessive or systemic inflammatory activation. Furthermore, in some specific types of cancer, the cGAS-STING pathway may be silenced due to gene or epigenetic inhibition, and the response to direct STING agonists is limited [38]. These limitations suggest that the new generation of agonists must go further in terms of bioavailability and tumor specificity, and also be combined with immune checkpoint inhibitors, DNA damage repair therapy, PARP inhibitors and epigenetic modifiers for combination therapy. In turn, in some cancers with persistent chromosomal instability and chronic inflammatory signals, therapeutic inhibition of STING activity may be a potential strategy to limit tumor supportive inflammatory processes (such as non-classical NF-κB pathway and IL-6-STAT3 signaling). Therefore, the treatment goal should not only stop at activating or inhibiting one or the other, but also regulate the intensity, duration and cellular localization of the pathway in a context-dependent manner. Future treatments need to identify such cancers first: genomic instability is sufficient to produce immunogenic DNA, the cGAS-STING pathway is intact, and the immune microenvironment can also respond to pathway activation. What these methods do is enhance protective anti-cancer immunity while suppressing chronic or dysfunctional inflammatory signals.

## 7. Conclusion

Genomic instability can lead to abnormal accumulation of cytoplasmic DNA, which is sensed by cGAS and activates the STING pathway, thereby initiating an anti-cancer immune response. Cancer cells also have countermeasures - degradation of cGAMP, silencing of cGAS / STING, and removal of cGAMP from the cell, all bypassing this set of monitoring. In turn, chronic STING activation may contribute to inflammation, immune escape and metastasis. Therefore, the treatment depends on the lesion: the pathway is active, immune and ' cold ' tumors, suitable for deactivating cGAS-STING; cancer driven by chronic STING-mediated inflammation should be considered for its inhibition. STING agonists, ENPP1 / TREX1 inhibitors, epigenetic modifiers, and rational combination with checkpoint inhibitors or DNA damage therapy have shown potential, but precision is still an unavoidable problem. The goal is not to simply turn cGAS-STING on or off, but to get the balance back-acute protective immunity to be enhanced, and chronic cancer-promoting inflammation to be avoided. In the future, it is necessary to rely on the identification of biomarkers and to understand the regulatory mechanism of cGAS-STING in different cancer stages.

DOI: 10.54254/2753-8818/2026.38717

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