

Targeting the cGAS–STING Pathway in Cancer Therapy: A Quantum Biology Perspective on Aging and Anti-Aging Strategies

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Abstract: The cGAS–STING pathway is composed of cyclic GMP-AMP synthase (cGAS) and the stimulator of interferon genes (STING). It plays a critical role in detecting DNA damage and activating the innate immune system for pathogen defense. The pathway has been extensively studied for its potential in cancer therapy, aiming to enhance anti-tumor immunity. However, emerging evidence indicates that cGAS–STING signaling can also contribute to inflammatory carcinogenesis. Key side effects include autoimmune and inflammatory reactions, as well as tissue tumorigenesis, which may limit the therapeutic benefits of type I interferon (IFNs) and cGAS–STING modulation strategies. This review also highlights that integrating proteomics, genomics, and transcriptomics could improve our understanding of the cGAS–STING pathway. Such approaches may facilitate drug development, including novel drug design and targeted delivery. Nevertheless, their efficacy must be validated through rigorous preclinical in vivo studies and early-phase clinical trials. This review provides a comprehensive overview of the cGAS–STING pathway in cancer therapy, highlighting its therapeutic potential and associated risks. We examine the dual role of cGAS–STING in tumor suppression and inflammatory carcinogenesis, discuss side effects such as autoimmune reactions, and explore how multi-omics approaches, including proteomics, genomics, and transcriptomics, can enhance our understanding of this pathway.

Keywords: cGAS-STING pathway; cancer therapy; aging and antiaging; anti-tumor effects

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1. Introduction

1.1. cGAS-STING function.

The cGAS–STING pathway plays a crucial role in detecting cytosolic DNA and invading pathogens, initiating inflammatory gene expression that can lead to cellular senescence or activate defense mechanisms. While DNA is primarily confined to the nucleus, it can also be present in the cytosol, a phenomenon associated with tumorigenesis and viral

infections [1,2]. cGAS is localized both in the cytosol and nucleus. In the nucleus, portions of cGAS are tightly bound to chromatin to prevent activation by self-DNA, while cytosolic cGAS recognizes DNA to activate the production of interferon-beta (IFN- β) [1–3]. The cGAS–STING pathway operates by detecting cytosolic DNA and inducing an immune response. Upon DNA binding, cyclic GMP-AMP synthase (cGAS) catalyzes the formation of cyclic GMP-AMP (cGAMP) from GTP and ATP. cGAMP then binds to the stimulator of interferon genes (STING), triggering the phosphorylation of interferon regulatory factor 3 (IRF3) via TBK1. Activated IRF3 translocates to the nucleus to induce transcription of IFN- β and other inflammatory genes [2,3]. This pathway is essential for mediating immune defense against double-stranded DNA viruses. It also contributes to type I interferon (IFN-I) production and inflammatory responses, often through autophagy—a homeostatic process with multiple effects on innate immunity. However, direct mechanistic links between cGAS–STING signaling and autophagy remain incompletely defined [3,4]. cGAS and STING have been shown to influence non-canonical autophagy through interactions with LC3 via the LC3-interacting region. Autophagy regulated by the cGAS–STING pathway plays critical roles in innate immune responses, maintaining cellular homeostasis, reducing liver damage, and inhibiting tumor growth [3,4]. Pattern recognition receptors (PRRs) within the innate immune system recognize pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), such as cytosolic DNA. Detection of these nucleic acids by PRRs activates immune-response genes [4,5]. Cytosolic DNA is sensed primarily by cGAS, which dimerizes upon binding DNA and produces cGAMP. cGAMP activates STING, leading to phosphorylation of IRF3 via TBK1, nuclear translocation, and transcription of IFN- β and other inflammatory genes [5,6]. PRRs detect abnormal signals, allowing DNA recognized as PAMPs or DAMPs to initiate innate immune responses against damaged or malignant cells [1,2]. The cGAS–STING pathway can evaluate both self and non-self DNA, including microbial DNA released from mitochondria, the cytosol, or abnormal chromosomal DNA. Following activation, STING moves from the endoplasmic reticulum to the ER–Golgi intermediate compartment (ERGIC), where it assembles into large oligomeric complexes. These oligomers recruit TBK1, which phosphorylates serine 366 (human) or 365 (mouse) in the C-terminal domain, creating an active site for IRF3 [6–10]. Activated IRF3, often in complex with TBK1, moves to the nucleus to induce IFN-I production, while nuclear factor κ B (NF- κ B) is also activated via the IKK pathway [10]. Recent studies indicate that the cGAS–STING pathway not only drives IFN-I and inflammatory responses but also modulates autophagy across a range of organisms, including mammals, *Drosophila*, and sea anemones [1,11]. Autophagy activation via cGAS–STING is particularly evident in aneuploidy-associated conditions, such as Down syndrome [12]. In herpes simplex virus type 1 (HSV-1) infected mouse embryonic fibroblasts, HSV-1 enhances LC3 puncta formation and autophagic flux through this pathway [13]. Similarly, Zika virus infection in *Drosophila melanogaster* brains induces LC3 lipidation via STING-mediated autophagy, preventing viral proliferation [14]. These findings suggest that autophagy is a primordial and evolutionarily conserved function of the cGAS–STING pathway, which preceded type I interferon signaling. For instance, STING from *Nematostella vectensis* triggers autophagy without inducing interferons via cGAMP [8]. Mechanistically, autophagy can be induced by cGAS directly in the absence of STING during DNA virus infections [15,16], while other studies report STING-dependent autophagy following cGAMP stimulation [13,17]. Conflicting evidence also exists regarding canonical versus non-canonical autophagy pathways activated by cGAS–STING [13,18]. This raises a key question in the field: How does

the cGAS–STING pathway regulate autophagy? In this review, we aim to address this question by summarizing current evidence and proposed mechanisms (Figure 1).

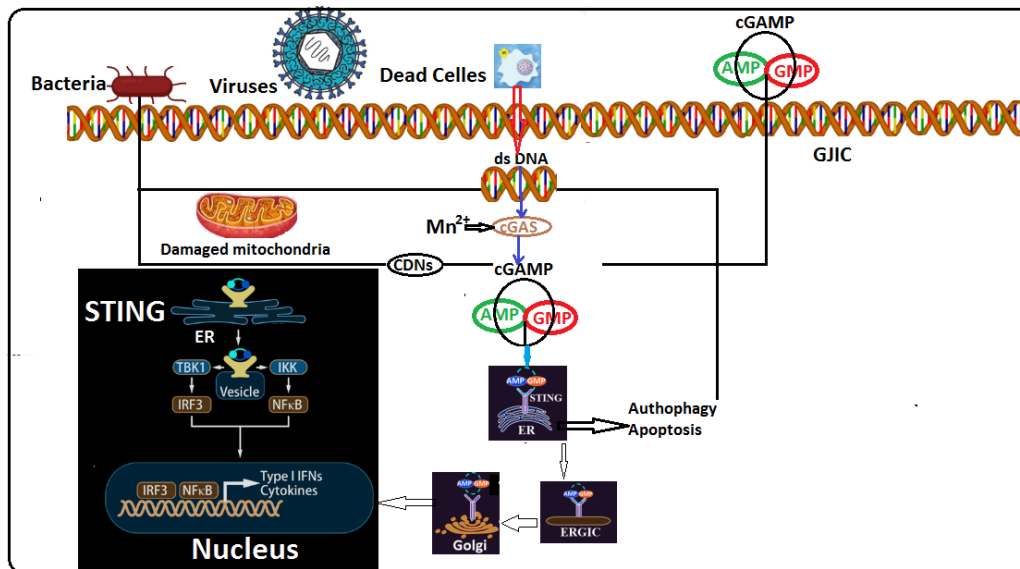


Figure 1. A schematic of the cGAS–STING pathway. cGAS can be activated by dsDNA, with Mn^{2+} also enabling cGAS activation. cGAMP binds to STING dimers located at the ER membrane, leading to changes in STING. STING can also be activated through cGAMP from bacterial and GJIC sources. Consequently, STING translocates from the ER to the Golgi apparatus via ERGIC. During transportation, STING interacts with TBK1, which contributes to phosphorylation at the C-terminal side and prepares an activated site for IRF3, ultimately inducing type I IFN.

1.2. Agonists and cGAS–STING pathway.

It is known that the cGAS-STING pathway connects innate and adaptive immunity for killing tumor cells [19, 20]. There are two pathways of activation, direct and indirect, which can stimulate anti-tumor immune reactions. Although indirect agonists cannot directly activate STING, they trigger a series of reactions that lead to the activation of the cGAS-STING pathway. The indirect pathway consists of several mechanisms for cancer therapy, including DNA-damaging chemotherapies [21], camptothecin [22], doxorubicin [23], paclitaxel [24], and etoposide [25,26]. Several activations can be affected by perturbations in DNA structures, ultimately leading to the killing of the response action using poly ADP-ribose polymerase (PARP) [27,28], ataxia telangiectasia and rad3-related (ATR) inhibitors [29], as well as radiation [30]. The activation inside tumor cells is initiated by cellular dsDNA from cGAS, with agonists attaching to STING directly, supporting memory T cells in participating in long-lasting immune responses against tumors [19]. In addition, cGAS-STING agonists stimulate the release of chemokines in an IFN-I response [31], which allows for the infiltration of $CD8^{+}$ T cells into the cancer tumor, leading to an effective anti-tumor immune response [20].

When STING is activated in cancer cells, it begins producing IFN- β , which causes a downregulation of MHC-I expression. This leads to the evasion of tumor cells from immune detection by cytotoxic T-lymphocytes (CTLs) [32]. The multiple effects of cGAS-STING agonists indicate that they have the potential to act as anti-cancer systems (Figure 2).

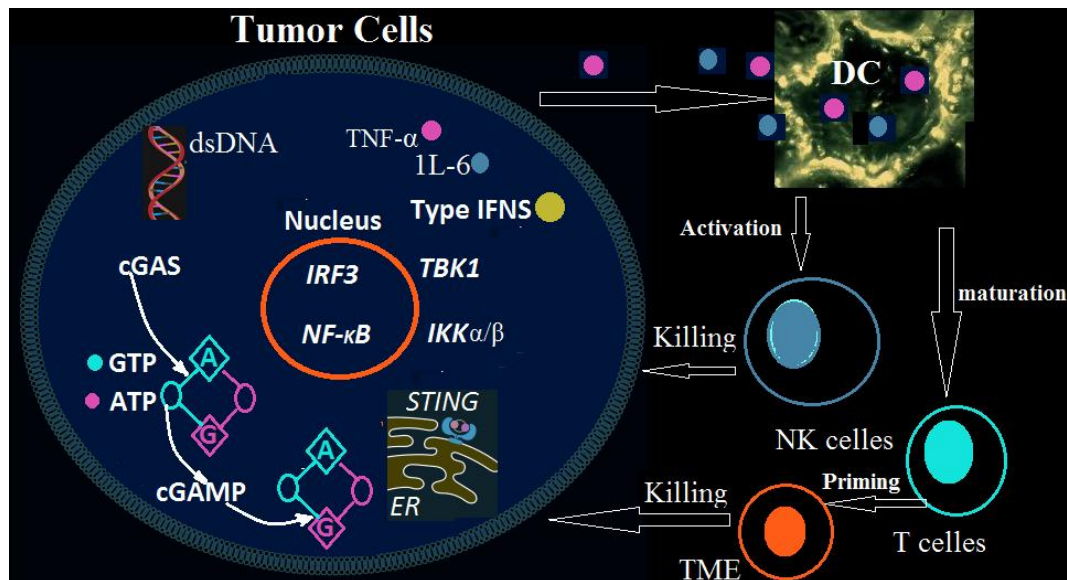


Figure 2. cGAS-STING agonists increase IFNs and maturation of DCs through the cGAS-STING pathway, activating T cells and NK cells.

1.3. Cyclic di-GMP, di-AMP, and cGAM.

These are all cyclic dinucleotides (CDNs) that, after activation by DNA, enable the synthesis of cGAMP to start. cGAS acts as a catalyst in activating the STING-mediated IFN-I response [33]. Based on the direction of phosphodiester bonds, it can be concluded that cGAMP has canonical or non-canonical structures. In other words, canonical CDNs have a 3',3' linkage direction arising from bacteria; however, they have mostly been ignored as a suitable drug due to weak effects on activating the STING isoforms and translation restrictions [34]. On the other hand, non-canonical CDNs have high potential for drug design. They have synthetic shapes like 2',2'-cGAMP, which has two 2',5' phosphodiester bonds; 3',2'-cGAMP, confirmed as a product of cGAS-like for identifying dsRNA; and 2',3'-cGAMP, created intracellularly by mammalian cGAS with high affinity for all human STING [35-38]. The sequence affinities for human STING are as follows: 2',3'-cGAMP > 2',2'-cGAMP > 3',3'-cGAMP ≈ 3',2'-cGAMP [39,40]. The binding interactions and detailed orientation of cGAMP within STING can be seen in Figure 3 [40]. Although native CDNs are weak agonists due to their susceptibility to hydrolytic destruction by phosphodiesterases, they provide a foundation for the design of STING agonists. Recently, scientists have made efforts to investigate improved CDNs and non-nucleotide small molecules (Figure 3) as synthetic agonists for human STING. Researchers have focused on synthetic CDN analogs that do not undergo hydrolysis and consist of 2',5' and 3',5' phosphorothioate bonds, similar to the structures of native CDNs such as 3',3'-cGAMP and 3',2'-cGAMP.

As seen in Figure 4, the structure of (i) is the first STING agonist used in clinical treatment. It has a high affinity for both mouse STING and human STING, which enhances the production of IFN-I significantly. The phosphorothioate bonds increase lipophilicity and stability, while replacing one oxygen atom with sulfur in the P-S bridge increases resistance to phosphodiesterase degradation, improving cellular uptake and cytosolic delivery [45-48]. Structure (ii) has high potential for STING activation in both top and down squamous cell carcinoma and has been used for clinical treatment [49]. Structure (iii) exhibited anticancer effects in mice with a high ability to create cancer immune memory.

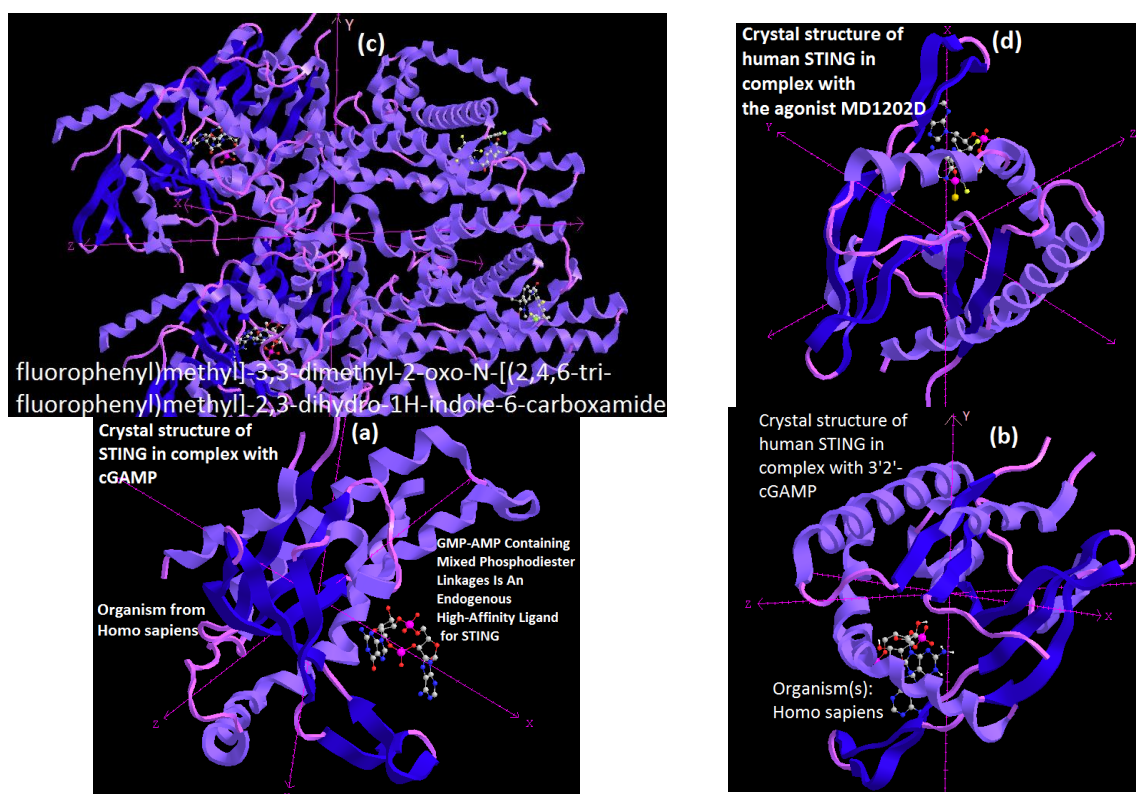


Figure 3. (a) Cyclic GMP-AMP containing mixed phosphodiester linkages acts as an endogenous high-affinity ligand that binds to STING [41]; (b) Structural basis underlying the specific recognition of metazoan cyclic GMP-AMP by the innate immune adaptor protein STING [42]; (c) Activation of STING by targeting a pocket in the transmembrane domain [43]; (d) Fluorinated cGAMP analogs, which act as STING agonists and are not cleavable by poxins: Structural basis of their function [44].

To improve therapeutic performance, transannular macrocyclic bridges were applied to improve the stability of the CDNs in their active sites of U-shaped structures [50,51]. Since the analog synthesis of endogenous CDNs is essential for clinical treatment with CDN agonists, various challenges may arise, including weak metabolism, low cellular uptake, and limited utilization [52]. Although there have been various clinical investigations on cancer drug delivery, most industrial syntheses of CDNs do not provide enough information. These limitations can be addressed through simulation and modeling before any synthesis takes place to improve the performance of delivery systems and drug design.

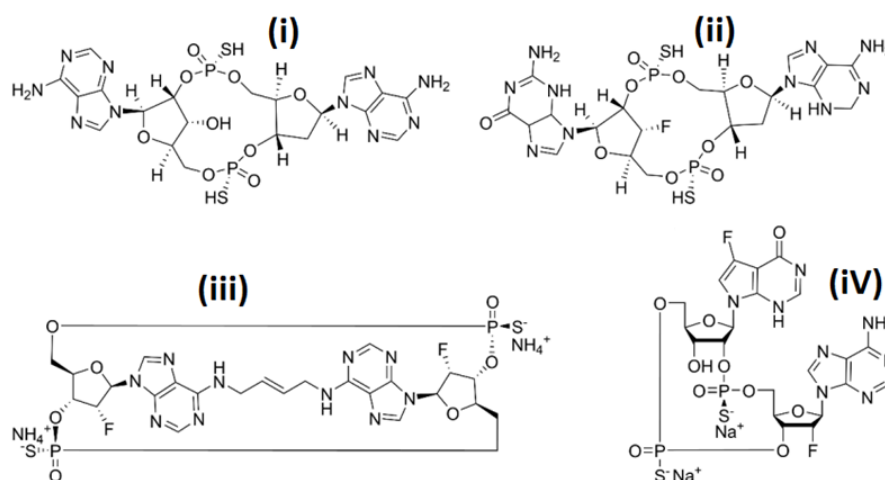


Figure 4. Various CDN human STING agonists. Structure (i) is the first STING agonist used in clinical treatment; Structure (ii) has high potential for STING activation in both top and down squamous cell carcinoma; Structure (iii) exhibited anticancer effects in mice with a high ability to create cancer immune memory; Structure (iv) exhibited the CDNs in their active sites of U structure.

1.4. Autophagy and cancer therapy.

Autophagy is a fundamental cellular process in which cells degrade and recycle damaged organelles, unfolded proteins, and other cytoplasmic components through lysosomes. This self-digestion mechanism helps maintain cellular homeostasis, provides energy during nutrient stress, and protects cells from damage caused by reactive oxygen species or DNA instability. There are three main types of autophagy: macro-autophagy, micro-autophagy, and chaperone-mediated autophagy, each with distinct mechanisms for degrading cellular components. In the context of cancer, autophagy plays a dual and complex role. On one hand, it acts as a tumor suppressor by removing damaged organelles and limiting oxidative stress and genomic instability, thereby preventing malignant transformation. On the other hand, in established tumors, autophagy can promote cancer cell survival by providing nutrients and energy under stressful conditions, such as hypoxia or chemotherapy. This duality makes autophagy a key target in cancer therapy. Cancer therapy encompasses various strategies to control or eliminate tumor cells, including surgery, radiation, chemotherapy, targeted therapy, and immunotherapy. Several therapeutic approaches aim to manipulate autophagy: inducing autophagy in certain contexts can trigger cancer cell death, while inhibiting autophagy can prevent tumor cells from surviving stress caused by treatment. Understanding the precise regulation of autophagy in different cancer types is therefore critical for developing effective therapies and improving patient outcomes.

Finally, this review provides a comprehensive overview of the cGAS–STING pathway, focusing on its roles in DNA sensing, immune activation, and autophagy regulation. We examine its dual impact on cancer development and therapy, summarize the current mechanistic understanding of autophagy induction, and highlight gaps in knowledge that warrant further investigation. By integrating current findings, this review aims to guide future research toward safely modulating cGAS–STING for cancer therapy while minimizing adverse effects, offering insights into both aging and anti-aging strategies.

2. cGAS–STING Pathway Regulation

There are two signals in the regulation of the cGAS-STING pathway, one positive and one negative, which depend on cellular molecules, enzymes, and other DNA-sensing reactions. The negative signal, omitting cytosolic DNA, prevents cGAS activation. Several cellular nucleases can play a role in this process, such as DNase II, an enzyme specialized in DNA digestion in endosomes. This enzyme creates a barrier to prevent DNA from leaking into the cytosol [53]. Similarly, an important function of DNase III is to remove excess double-stranded DNA in the cytosol [54]. Additionally, the RNase family group, composed of RNaseH2A, RNaseH2B, and RNaseH2C, is responsible for separating ribonucleotides embedded in DNA from RNA/DNA hybrids. This process occurs during DNA replication and simultaneously establishes a barrier that restricts the release of abnormal DNA into the cytosol [55]. The other nuclease has a SAM domain containing an HD domain, is best known as a dNTPase, and inhibits reverse transcription of RNA in bacteria. In addition, activated SAMHD1 can also enhance its enzymatic potential to prevent the accumulation of single-stranded DNA fragments in the cytosol [56]. As a result, an incomplete function of endonucleases, especially DNase II, RNaseH2, and SAMHD1, can lead to an abnormal accumulation of dsDNA, resulting in an excessive activation of the cGAS-STING pathway. In contrast to the above endonucleases, other DNA components can modulate the cGAS-STING pathway in a negative manner. For

example, the IFI16 protein is a member of the PYHIN family and acts as a sensor for invading DNA viruses, as well as damaged chromatin DNA in any nucleus and cytosol. By detecting DNA, IFI16 initiates the STING-dependent type I IFN signaling pathway, which is related to TRAF6 and p53 [57]. Recent research has also confirmed that IFI16 competes for attachment to DNA and STING, somewhat regulating cGAMP. Thus, IFI16 is necessary for the higher-level reactions of STING [58,59]. In addition, the HIN2 domain of IFI16 inhibits cGAS when a portion of cGAS is able to enter the nucleus and maintains the stability of IFI16 [60,61]. AIM2 is another DNA sensor in the PYHIN group located in the cytosol. After detecting dsDNA, AIM2 interacts with apoptosis-associated proteins such as CARD (ASC) and procaspase-1 to create inflammasomes [62]. This triggers a multi-protein signaling cascade that activates caspase-1 and leads to the maturation and release of IL-1 β and IL-18, ultimately resulting in pyroptosis [63]. The downstream ligands of cGAS, containing cGAMP and STING, enable the regulated potential of cGAS through negative modulation, such as deubiquitination, glutamylation, phosphodiesterase-catalyzed hydrolysis, sumoylation, and phosphorylation. Additionally, cGAS potential can be modified by direct protein-protein interactions, allowing intracellular factors to modulate cGAS activities. Table 1 lists cellular components that can disrupt cGAS, cGAMP, or STING activity through modification or degradation [64-69].

Table 1. Degradation agents of the cGAS, cGAMP, and STING activities.

Aims and purpose	Modulators	Improving and correcting	Mechanisms	References
cGAS	Caspase-1	degradation	Decreased type-I IFN	[65]
	AKT	Phosphorylation	Phosphorylation of cGAS	[70]
	BTK	-	Decreasing performance in attaching to DNA	[71]
	TRIM38	Sumoylation	Controls cGAS activation in the absence of microbial invasion	[72]
	TTLL6	Polyglutamylation	Barrier activation for cGAS–DNA synthesis	[73]
	TTLL4	Monoglutamylation	Reducing the activation of the enzymatic cGAS	[73]
	Cia-cGAS	Straight binding	Barriers in the binding of cGAS to DNA	[74]
cGAMP	OASL	Straight binding	Reducing the activation of cGAS synthesis	[75]
	ENP11	Phosphodiesterase	Hydrolyzes cGAMP	[76]
STING	USP13	Deubiquitylation	Barriers to the absorption of TBK1 by STING	[77]
	NLRC3	Straight binding	Destroying the binding forces between STING and TBK1	[78]
	NLRX1	Straight binding	Destroying the binding forces between STING and TBK1	[79]
	ULK1	Phosphorylation	Sustainable product of type I IFN through STING	[80]
	RNF5	Ubiquitylation	Dissociates the STING components at mitochondria	[81]
	AP-1	Straight binding	Finalization of the sequencing of STING in the Golgi	[82]
	2-BP	Straight binding	Inhibit the palmitoylation of STING in the Golgi	[83]

Modulators primarily positively regulate the cGAS-STING pathway through post-translational steps, including modifications, direct reactions, and indirect mechanisms. A list of these modulators is provided in Table 2.

Table 2. Modulator items cause an increase in cGAS, cGAMP, and STING activities.

Aims and purpose	Modulators	Improving and correcting	Mechanisms	References
cGAS	SENP7	Desumoylation	Sumoylated broken cGAS for enhancement potential	[84]
	HDAC3	Deacetylation	Increases the potential of cGAS	[85]
	RNF185	E3 ubiquitylation	Increases the catalytic potential of cGAS.	[86]
	Mn ²⁺ ion	Straight binding	Enhancements to cGAMP–STING binding strength	[87]
	G3BP1	Straight binding	Essential for the high-impact potential of cGAS	[88]
	R848	Non-straight binding	Detecting HIV-1 virus through cGAS	[89,90]
	PAM3	Non-straight binding	Detecting HIV-1 virus through cGAS	[89,90]
	TRIM41	Monoubiquitylation E3 ubiquitylation	Increasing the potential of cGAS versus viral infection prevents cGAS from being destroyed by autophagy.	[91,92]
cGAMP	Zn ²⁺ ion	Straight binding	increases the velocity of cGAS–DNA synthesis for liquid-phase condensation	[93]

Aims and purpose	Modulators	Improving and correcting	Mechanisms	References
STING	AMFR	E3 ubiquitylation	Facilitates TBK1 adsorption by STING and its translocation.	[94]
	MUL1	Polyubiquitylation	Promotes STING trafficking	[95]
	TMEM203	Straight binding	Collaborates with STING to increase TBK1 and IRF3 potential	[96]

3. Treatment Process According to the cGAS–STING Pathway

As outlined in this overview, the cGAS–STING pathway plays a central role in the pathogenesis of numerous diseases, making it a valuable therapeutic target. For instance, inhibitors that suppress the cGAS–STING pathway may help slow the progression of autoimmune disorders and inflammation. Conversely, agonists that enhance this pathway can modulate immune responses and limit the spread of extracellular pathogens. Accordingly, STING agonists have potential applications as vaccines against infectious viruses. In cancer therapy, tumor immunotherapy targeting the cGAS–STING pathway must consider several factors, including immune status, the level of pathway activation, cancer cell type, and tumor location. Proper activation of the pathway in immune cells can yield beneficial effects, such as controlling tumor growth. However, excessive activation may promote carcinogen-induced cancers and impair T cell–mediated immunity [97]. Thus, careful evaluation of the cancer context is essential when exploring the use of cGAS–STING agonists in tumor immunotherapy. Additionally, maintaining cGAS and STING activity within physiological levels is crucial to maximize anti-cancer effects while minimizing side effects. This underscores the therapeutic promise of developing STING agonists as cancer vaccines [98]. Inhibitors of the cGAS–STING pathway can be divided into two main classes: cGAS inhibitors and STING inhibitors. cGAS inhibitors include catalytic site blockers, which target the enzyme’s active site and DNA-binding region. By preventing cGAS from interacting with double-stranded DNA (dsDNA), these inhibitors disrupt its catalytic function. STING inhibitors, in contrast, typically target the cyclic dinucleotide (CDN) binding site as competitive antagonists. Some also act as palmitoylation inhibitors, binding to STING’s palmitoylation sites to reduce downstream signaling and inhibit activation. Table 3 lists the properties and biological activities of these inhibitors. Research on the cGAS–STING pathway has focused primarily on STING agonists because of their anti-tumor potential. These include CDNs, non-CDNs, and indirect agonists [99]. Table 3 also lists common STING agonists and their primary effects [100–104].

Table 3. Inhibitors and agonists of cGAS and STING.

Materials	specifications	Biological consequences	References
cGAS inhibitors			
PF-06928215	Attached to cGAS active sites and ATP place	Type-I IFN is reduced in AGS mouse samples	[105,106]
RU.521	Has been placed over the catalytic site of cGAS	decreasing expression and transcription of Ifnb1 in BMDMs	[107]
G150	Attached to the cGAS active site	0.65 μ M IC50 in macrophages (H)	[108]
CU-76 CU-32	cGAS dimerization inhibiting	Particular objective for cGAS–STING inhibition	[109]
Aspirin	Residues Lys384, Lys394, and Lys414 of cGAS	Destroying AGE-related mouse samples	[85]
Compound C	Decreasing cGAMP population	Destroying type-I IFN	[110]
DNA-binding inhibitors			
AMDs	cGAS–dsDNA blocked Interaction	5–30 μ M of the IC50 in THP-1	[111,112]
Suramin	Prevention of the cGAS–dsDNA complex formation	Modifying and keeping the amount of type I IFN inside the THP-1	[113]
A151	Attached to the DNA of cGAS	Control signaling from type-I IFN in the absence of the TREX1 cells	[114]

STING inhibitors			
Astin C	Controller and inhibitor of the activation of IRF3 from the STING-TBK1	Controller and inhibitor of IRF3 from the STING-TBK1 of the mouse Ifng, Cxcl0, and Tnf mRNA in the expression and transcription	[115]
THIQ	Convert STRING into an open and inactive compound	cGAMP of the type-I IFN in THP-1 inhibitor	[116]
Nitrofurans	Attaching to Cys91 for the palmitoylation of the STING inhibitor	Strongly controlling and destroying the inflammatory response in mouse samples	[117]
Indole urease	Creating a covalent bond with Cys91 of STING	Decreases type-I IFN amount in mouse cancer of TREX1	[117]
NO2-FAs	Modifying and Modulating the Covalent Bond of Cys88 and Cys91 in STING	cGAMP-induced type-I IFN was inhibited in THP-1 cells	[118]
Agonists of STING (CDN agonists)			
Natural CDNs	Activation of the APCs and CD8+	Increasing antitumor signals	[119]
ADU-S100	STING activation for increasing stability	tumor regression	[119]
cGAMP-NPs	Liposomal NPs in cGAMP to increase performance	microenvironment application in anti-tumor	[120]
Non-CDN agonists			
DMXAA	High affinity of cGAMP for activating STING performance	Restricts tumorigenesis	[121]
Zebularine	STING gene transcription by demethylation	Decreasing tumor burden	[122]
G10	Stabilizes the structure of STING	Preventing tumor growth	[123]
ABZI	Type-I IFN produces four hundred times more than that of cGAMP	Tumor volume regression	[124]
DSDP	STING-related cytokine reactions	Triggers antiviral responses	[125]
BNBC	Specifically activates STING	Triggers antiviral reactions	[126]
Indirect agonists			
Radiotherapy	Making DSBs and the accumulation of cytosolic DNA	Increasing the potential of the immune reaction	[127]
Cisplatin	DDR inhibitors prevent the release of chromatin fragments inside the cytosol	Increasing the potential of the CD8+ T cells	[57]
Teniposide	Causing DNA destruction in the tumor	Increasing the potential of the DCs and T cells	[128]

4. cGAS/STING Pathway in Carcinogenesis

The cGAS/STING pathway is primarily targeted to enhance its potential in cancer treatment. However, research results indicate that the cGAS/STING pathway also contributes to inflammatory carcinogenesis. Major side effects include autoimmune and inflammatory reactions, as well as tissue tumorigenesis, which limit the anti-tumor effects of type I interferons (IFNs) and cGAS/STING signaling modulation therapy. Activation of STING has been shown to increase the production of inflammatory cytokines by infiltrating phagocytes, thereby promoting inflammation-driven carcinogenesis. In mice, STING deficiency confers significant resistance to mutagen-induced skin carcinoma compared with wild-type mice. Additionally, DNA sensing through the cGAS/STING pathway can induce tolerogenic responses in mice [129] by activating immune regulatory mechanisms. Indoleamine 2,3-dioxygenase (IDO) is an important immune regulator. STING signaling can induce and activate IDO within the cancer microenvironment [130-132]. In addition, it has been shown to promote the growth of Lewis lung carcinoma (LLC). Conversely, deleting STING increases CD8+ T cell infiltration and tumor cell killing while reducing suppressor cell infiltration and IL-10 expression in cancer cells. These findings indicate that STING signaling plays a role in attenuating CD8+ T cell function during tumorigenesis [133-136]. Molecular insights into virus-associated carcinogenesis have improved understanding of the cGAS/STING pathway. In addition, transcription of STING has been shown to be upregulated in HPV-positive tongue squamous cell carcinoma (TSCC), increasing STING activity. This induction promotes the

expression of several immunosuppressive cytokines and chemokines, facilitating regulatory T-cell infiltration and contributing to carcinogenesis by suppressing effective anti-cancer immune responses [137]. Research results confirm that self-DNA-mediated activation of the cGAS/STING pathway is important in autoimmune and inflammatory diseases. Given current knowledge of genome instability, DNA damage, and nuclear DNA dysregulation in cancer, the cGAS/STING pathway can also be activated during inflammation-driven carcinogenesis. Notably, the carcinogenic effects of cGAS/STING signaling appear to be cancer type-dependent. For example, STING^{-/-} mice were resistant to DMBA-induced skin carcinoma [138]. Therefore, cancer type, anatomical location, tissue specificity, and the tumor microenvironment may play critical roles in determining whether the cGAS/STING pathway exerts anti-cancer or pro-carcinogenic effects. Finally, Preclinical evidence refers to scientific findings obtained before testing in humans. It is generated through laboratory experiments using cell cultures (in vitro studies) and animal models (in vivo studies). The primary purpose of preclinical research is to understand biological mechanisms, evaluate preliminary effectiveness, assess toxicity, and determine safe dosage ranges. While preclinical evidence helps establish biological plausibility and safety profiles, it does not confirm that a treatment will work in humans. Clinical evidence, in contrast, is derived from research conducted in human participants. This includes observational studies and clinical trials (Phase I–IV). Clinical research aims to evaluate safety, determine effectiveness, monitor side effects, and compare treatments in real-world human populations. Clinical evidence provides direct information about how a therapy performs in people and is necessary for regulatory approval and medical use.

In summary, preclinical evidence addresses whether a treatment could work and appears safe based on laboratory and animal data, whereas clinical evidence determines whether the treatment works and is safe in humans.

4.1. Mitochondrial dysfunction.

Mitochondrial dysfunction refers to the progressive loss of mitochondrial efficiency and integrity over time. Mitochondria produce ATP through oxidative phosphorylation, regulate apoptosis, maintain calcium homeostasis, and generate metabolic intermediates. During aging, mitochondria accumulate damage to mitochondrial DNA (mtDNA), proteins, and lipids—largely due to reactive oxygen species (ROS) generated during respiration. Impaired mitochondrial quality control mechanisms, such as mitophagy and biogenesis, further exacerbate this damage. As dysfunctional mitochondria accumulate, ATP production declines and oxidative stress increases. Damaged mitochondria may also release mitochondrial DNA into the cytosol, where it can act as a danger-associated molecular pattern (DAMP) and activate inflammatory pathways such as cGAS–STING. Consequently, mitochondrial dysfunction not only reduces cellular energy capacity but also promotes chronic inflammation and tissue degeneration. Genomic instability refers to the accumulation of DNA damage and mutations within the nuclear genome over time. Sources of genomic instability include replication errors, oxidative damage, telomere shortening, environmental stressors, and defective DNA repair mechanisms. Cells possess multiple DNA repair pathways (e.g., base excision repair, homologous recombination), but these systems become less efficient with age. Persistent DNA damage can lead to chromosomal rearrangements, mutations, and telomere attrition. When DNA damage exceeds repair capacity, cells may enter senescence or undergo apoptosis. Additionally, fragments of damaged nuclear DNA can accumulate in the cytoplasm, where

they activate innate immune sensors such as the cGAS–STING pathway, contributing to chronic low-grade inflammation.

Importantly, mitochondrial dysfunction and genomic instability reinforce one another. Increased ROS from damaged mitochondria can further damage nuclear DNA, while genomic instability can impair genes involved in mitochondrial maintenance and repair. This creates a self-amplifying cycle of cellular damage, inflammation, and functional decline.

Together, mitochondrial dysfunction and genomic instability are not merely markers of aging but active drivers of age-associated pathology. Their interaction contributes to cellular senescence, stem cell exhaustion, chronic inflammation, and increased susceptibility to neurodegenerative diseases, cancer, and metabolic disorders. Understanding these processes is essential for developing interventions that extend healthspan and restore cellular homeostasis.

5. Summary

The cGAS–STING pathway centrally mediates cytosolic DNA sensing and type I interferon (IFN-I) production, playing essential roles in antiviral defense and tumor surveillance. However, increasing evidence indicates that chronic activation of this pathway contributes to aging and age-related pathology. Aging is associated with genomic instability, mitochondrial dysfunction, defective autophagy, and accumulation of senescent cells—each of which promotes cytosolic DNA accumulation and persistent cGAS activation. Sustained STING signaling subsequently drives NF- κ B and IFN- γ responses, contributing to chronic low-grade inflammation. Cellular senescence represents a key mechanistic link between cGAS–STING activation and aging. Cytoplasmic chromatin fragments in senescent cells activate cGAS, reinforcing the senescence-associated secretory phenotype (SASP) and creating a pro-inflammatory feedback loop that promotes tissue dysfunction and stem cell exhaustion. Elevated pathway activity has also been implicated in neuroinflammatory conditions such as Alzheimer's disease and Parkinson's disease, as well as autoimmune diseases, including Systemic lupus erythematosus, further linking dysregulated DNA sensing to age-associated decline. Despite its role in inflammation, completely inhibiting cGAS–STING signaling may be detrimental. Moderate activation enhances immune surveillance and limits tumor genesis, a critical function given the increased cancer risk with age. Therefore, the impact of pathway modulation is context-dependent and likely varies by tissue type and activation magnitude. Collectively, these findings suggest that aging is driven not simply by cGAS–STING activation, but by its chronic dysregulation. Therapeutic strategies should aim to restore homeostatic balance, potentially through selective pathway inhibition, enhanced DNA clearance mechanisms, mitochondrial protection, or senolytic approaches, while preserving antiviral and anti-tumor immunity. Fine-tuning, rather than abolishing, cGAS–STING activity may therefore be a promising strategy to extend health span.

6. Concluding Remarks

In conclusion, the cGAS-STING pathway in various diseases requires further investigation and comprehensive characterization, particularly the detailed mechanisms of STING signaling, which holds great potential for treating many diseases. Scientists generally agree that, in the near future, deeper exploration of mechanisms across different cell types and tissues, as well as cancer progression mediated by the cGAS-STING pathway and its interactions with other signaling pathways, will support the development of combination

therapies. Such efforts will provide a stronger foundation for the discovery of novel cancer treatments. In addition, the application of proteomics, genomics, and transcriptomics may enhance our understanding of this pathway. These approaches could also advance drug development, including drug design and delivery; however, their effectiveness requires further validation through rigorous preclinical in vivo studies and early-stage clinical trials.

Author Contributions

Conceptualization, M.M., F.M., Ş.Z.H. and S.N.M.; methodology, M.M., F.M. and M.K.; software, M.M. and A.Y.; validation, M.M., F.M. and F.N.K.; formal analysis, M.M. and F.M.; investigation, M.M. and B.Ö.; resources, F.M., D.A., F.Y., K.S., S.S.A. and B.E.; writing—original draft preparation, M.M.; writing—review and editing, M.M. and F.M.; visualization, M.M., F.M., F.C.Ç. and M.K.; supervision, M.M.; project administration, M.M. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
AKT	RAC α Serine/Threonine-protein Kinase (Also Known as PKB)
BTK	Bruton's Tyrosine Kinase
ENPP1	Ectonucleotide Pyrophosphatase/Phosphodiesterase Family Member 1; TRIM38, Tripartite Motif
DNA	Deoxyribonucleic Acid
TTL6	Tubulin-tyrosine Ligase-like Member 6
TTL4	Tubulin-tyrosine Ligase-like Member 4
USP13	Ubiquitin Specific Peptidase 13
cia-cGAS	Circular RNA with Higher cGAS Affinity than dsDNA

Abbreviation	Definition
MRI	Magnetic Resonance Imaging
PCR	Polymerase Chain Reaction
OASL	Oligoadenylate Synthase
NLRC3	NOD-like Receptor Family 3 Containing CARD Domain
NLRX1	NLR Family Member X1
ULK1	Serine/Threonine UNC-51-like Kinase (ULK1/ATG1)
RNF5	RING Finger Domain; AP-1, Adaptor Protein, complex 1
2-BP	2-bromopalmitate
cGAS	Cyclic GMP-AMP Synthase
SEN7	Sentrin/SUMO-specific Protease 7
STING	Stimulator of Interferon Genes.
HDAC3	Histone Deacetylase 3
RNF185,	RING Finger, Protein 185
AMFR	Autocrine Motility Factor Receptor
MUL1	Mitochondrial E3 Ubiquitin Protein Ligase 1
G3BP1	GTPase-activating Protein SH3 Domain-binding Protein 1
TMEM203	Transmembrane Protein 203
R848	TLR7/8 Agonist
PAM3	TLR2 Agonist
TRIM41	Tripartite Motif Protein 41
cGAS	Cyclic GMP-AMP Synthase
STING	Stimulator of Interferon Genes.
BMDMs	Bone Marrow-derived Macrophages
IC50	Half-maximal Inhibitory Concentration
primary H-macrophages	Primary Human Macrophages
AMDs	Antimalarial Drugs (Such as Hydroxychloroquine And Quinacrine)
THP-1	Cells, Human Myeloid Leukemia Mononuclear Cells; THIQ
THIQ	Tetrahydroisoquinoline
NO2-FAs	Nitro Fatty Acids
cGAS	Cyclic GMP-AMP Synthase
type-I IFN	Type-I Interferon
AGS	Aicardi–Goutières Syndrome
IRF3	Interferon Regulatory Factor-3
TBK1	TANK-binding Kinase 1
CDNs	Cyclic Dinucleotides
APCs	Antigen-presenting Cells
cGAMP-NPs	cGAMP-nanoparticles
DMXAA,	5, 6-dimethylxanthenone-4-acetic acid
ABZI	Amide Benzimidazole;
DSDP	Dispiro Diketopiperazine
BNBC	6-bromo-N-(naphthalen-1-yl)benzo[d][1,3] dioxole-5-carboxamide
DSBs	Double-strand Breaks; DCs, Dendritic Cells

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