TMSJ
TURKISH MEDICAL STUDENT JOURNAL

Turk Med Stud J 2025;12(3):45-54
DOI: 10.4274/tmsj.galenos.2025.2025-5-1

REVIEW

IMMUNE ACTIVATION IN METASTATIC CANCERS: THE STING PATHWAY AND NANOPARTICLE-BASED THERAPEUTIC APPROACHES

Necla Duru Altınel

Hacettepe University School of Medicine, Ankara, TÜRKİYE

ABSTRACT

Cancer immunotherapy represents a significant treatment approach aimed at enhancing patient survival by targeting the tumor microenvironment and immune system. In recent years, considerable interest has been shown in novel therapeutic strategies that activate the immune system, particularly in patients with metastatic cancer. The stimulator of interferon genes pathway has been identified as a critical target due to its ability to enhance immune responses against malignancies. The stimulator of interferon genes adaptor protein plays a central role in cellular immune signaling and is an essential component of the deoxyribonucleic acid sensing machinery. Upon activation, the stimulator of interferon genes pathway induces the production of various cytokines, mainly type I interferons, to trigger an immune response in the tumor microenvironment. However, direct administration of stimulator of interferon genes agonists poses significant challenges due to systemic toxicity and off-target effects. To overcome these limitations, nanoparticle-based drug delivery systems have been developed to enhance therapeutic efficacy and minimize side effects. These systems enhance stimulator of interferon genes activation, ensure targeted distribution, and amplify immune stimulation. This review discusses the role of the stimulator of interferon genes pathway in metastatic tumors, the mechanisms underlying nanoparticle-based stimulator of interferon genes agonists, and recent findings from preclinical studies and clinical trials. Additionally, it discusses the advantages, challenges, and potential directions for future research on this approach.

Keywords: Immune activation, immunotherapy, metastatic cancers

INTRODUCTION

Cancer remains one of the leading causes of death worldwide (1). Metastatic cancers pose additional challenges as they frequently develop resistance to therapeutic agents (2). While the immune system can recognize and eliminate cancer cells, the tumor microenvironment (TME) typically employs immunosuppressive mechanisms that inhibit immune responses and allow tumors to evade immune surveillance (3). Consequently, there is a growing need for immunotherapeutic approaches that specifically target the innate immune system, a concept that has gained significant interest in recent years (4). Among these approaches, the stimulator of the interferon genes (STING) pathway has emerged as a valuable therapeutic target due to its ability to increase antitumor immune reactions (5). STING, an adaptor protein, is activated by cytosolic deoxyribonucleic acid (DNA), leading to the production of various cytokines, predominantly type I interferons (IFN-I) (6). This response initiates a strong immune response in the TME, thereby enhancing antitumor activity (7). STING activation not only triggers innate immunity but also enhances adaptive immune responses by priming cluster of differentiation 8^+ ($CD8^+$) T-cells for activation, which facilitates tumor-specific immunity (8). However, several tumor types suppress the STING signaling pathway, thereby limiting the effectiveness of immune activation (9). The development of pharmacological STING agonists has emerged as a strategy to overcome this limitation and enhance immune system function in cancer treatment (10). However, the direct application of STING agonists is limited by systemic toxicity and unexpected

Address for Correspondence: Necla Duru Altınel, Hacettepe University School of Medicine, Ankara, TÜRKİYE
e-mail: durualtinel2006@gmail.com
ORCID iD of the author: NDA: 0009-0005-0503-9988
Received: 25.05.2025 Accepted: 22.09.2025 Publication Date: 27.10.2025

Cite this article as: Altınel NC. Immune activation in metastatic cancers: the STING pathway and nanoparticle-based therapeutic approaches. Turk Med Stud J. 2025;12(3):45-54.

side effects (11). The use of nanoparticle-based drug delivery systems has emerged as a potential solution to overcome these limitations and improve treatment outcomes while minimizing unwanted effects (12). These nanoparticles are designed to increase STING activation, promote targeted delivery, and increase immune stimulation (13). Recent preclinical and clinical research has demonstrated promising findings regarding the use of nanoparticle-based STING agonists to treat metastatic cancers (14). This review will explore the involvement of the STING pathway in metastatic cancers, the development of nanoparticle-based STING agonists, their mechanisms of action, and their effects on immune responses, along with an examination of their advantages and disadvantages and future opportunities for nanoparticle-based STING activation.

1. STING Pathway and Immune Evasion Mechanisms in Metastatic Cancers

a) Escape mechanisms of metastatic cancers from the immune system

In metastatic cancers, immune evasion mechanisms are primarily triggered by acquired immune responses (15). The most significant mutations and genetic changes that contribute to this process occur during the early stages of tumor development (16). These include loss of heterozygosity, somatic mutations, and epigenetic changes that impair the presentation of neoantigens, programmed cell death ligand 1 (PD-L1) expression, and other immunosuppressive mechanisms (17, 18) (Figure 1).

b) The potential of STING to modulate the immune response

Stimulator of interferon genes activation has been shown to enhance the immune system's ability to recognize and eliminate metastatic tumor cells (19). This process involves a sequential five-stage cascade. Initially, the enzyme cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS) detects the accumulation of abnormal cytoplasmic DNA. cGAS then catalyzes the production of cyclic GMP-AMP (cGAMP), which acts as a second messenger activating STING. Once STING is activated, it triggers the release of damage-associated molecular patterns and tumor-specific antigens. These molecular signals are then recognized by dendritic cells, which are activated and subsequently prime T-cells. Finally, T-cells are activated to launch an immune response against cancer cells, thereby increasing the immune system's capacity to detect and destroy metastatic tumors (Figure 2) (20).

Within this immune-activating cascade, a sound rationale for combining STING agonists and immune checkpoint inhibitors (ICIs), particularly anti-programmed cell death protein 1 (anti-PD-1)/PD-L1 such as pembrolizumab or nivolumab, has been developed. While STING activation promotes dendritic cell maturation, enhances cross-presentation of tumor-derived antigens, and promotes T-cell priming and infiltration into the TME, ICIs operate at a later stage by maintaining T-cell effector function and preventing T-cell exhaustion (21). The STING agonists activate and amplify antitumor immune responses, whereas the ICIs act to sustain and maintain the immune response.

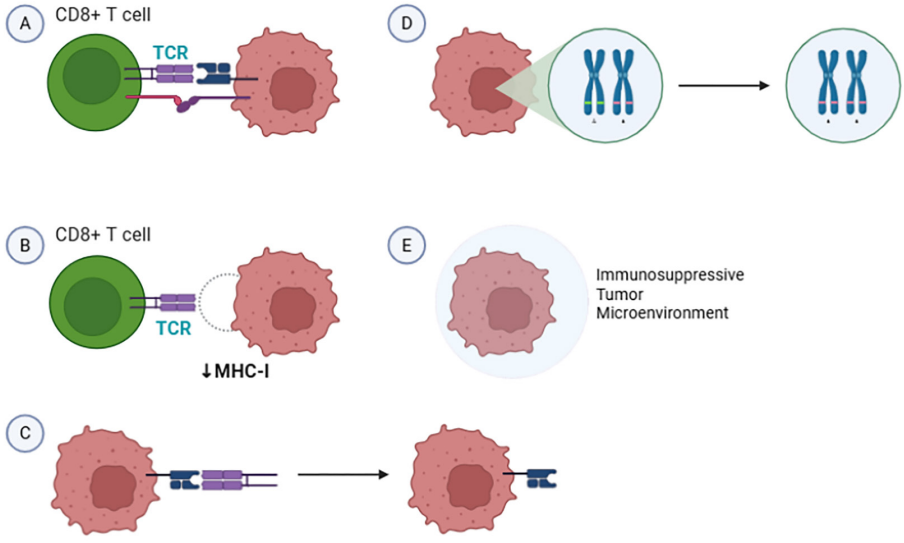


Figure 1: Mechanisms of immune evasion by metastatic cancers (created with BioRender.com).
Metastatic cancer cells employ various strategies to escape recognition and elimination by the immune system, often driven by acquired genetic and epigenetic changes during tumor development. A) Interaction between PD-1 on $CD8^+$ T-cells and PD-L1 on tumor cells inhibits T-cell activation and cytotoxic function, leading to immune evasion. B) Downregulation or loss of MHC class I molecules on tumor cells prevents antigen presentation, reducing $CD8^+$ T-cell recognition. C) Tumor cells may lose expression of immunogenic neoantigens due to selective pressure or mutations, hindering T-cell targeting. D) Genetic or epigenetic alterations in tumor cells can further impair antigen processing and presentation pathways. E) An immunosuppressive TME (e.g., presence of regulatory cells, cytokines, and metabolic factors) suppresses effective anti-tumor immune responses.
$CD8^+$: Cluster of differentiation 8^+, MHC: Major histocompatibility complex, PD-1: Programmed cell death protein 1, PD-L1: Programmed cell death ligand 1, TME: Tumor microenvironment, TCR: T-cell receptor

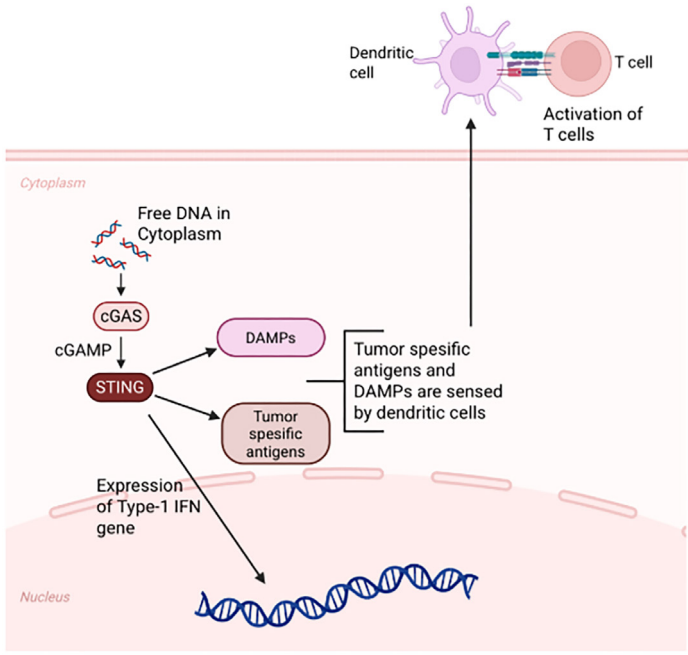


Figure 2: The cGAS-STING pathway and its role in anti-tumor immunity (created with BioRender.com).
This diagram illustrates the cGAS-STING pathway, a critical innate immune signaling cascade that detects cytosolic DNA and initiates anti-tumor immune responses.
cGAS-STING: Cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes, DNA: Deoxyribonucleic acid, IFN: Interferon, DAMPs: Damage-associated molecular patterns

Preclinical models have demonstrated that this dual approach can successfully "reprogram" immune "cold" tumors with poor T-cell infiltration that are resistant to checkpoint blockade into immune "hot" tumors in which immune cell trafficking, IFN signaling, and major histocompatibility complex-I expression are enhanced. These STING agonist-ICI combinations promote both the generation and persistence of effector T-cells, which lead to synergistic tumor regression with durable survival benefit (21).

Yet, this synergy may incur risks. The potentiated immune stimulation may result in a higher risk of immune-related adverse events (irAEs; e.g., colitis, hepatitis, pneumonitis, and systemic inflammatory syndromes). In addition, it is feasible that robust or continuous STING activation may trigger immune tolerance or cytokine storm-like effects that would counteract the anti-tumor effect (22). Therefore, additional focus on dose optimization, scheduling, and the integration of biomarkers for patient selection will be critical for safe or effective clinical translatability of combinations.

c) General evaluation of preclinical and clinical studies

The MIV-815 (ADU-S100) study, a clinical investigation conducted on the use of STING agonists in cancer immunotherapy, demonstrated that the immune system can be activated by injecting STING agonists directly into the TME (23). The study showed that MIV-815 was safe and able to trigger a systemic immune response. However, its clinical effectiveness was limited when used alone (23). This limitation highlights the difficulty of using a single treatment to overcome the immunosuppressive environment of a tumor and emphasizes the need for rationally designed combination regimens (24). Alternative methods of activating the STING pathway have also been explored. A preclinical study on Cadherin-11 (CDH11) inhibition found that this pathway indirectly activates STING signaling and enhances the immune system's response to tumor cells in metastatic cancers (24). The suppression of CDH11 has been shown to contribute to reducing tumor burden by increasing the activity of immune cells in the TME (25). However, this mechanism has only been validated in preclinical models, and further studies are required to assess its relevance in human cancers. A preclinical study also demonstrated that combining STING agonists with programmed cell death protein 1 (PD-1) inhibitors elicited a more robust immune response in metastatic tumors (26). This synergy potentiates T-cell responses by promoting dendritic cell activation within the TME. Although promising, the safety, timing, and dosage of such combination strategies require comprehensive clinical evaluation, particularly considering the risk of immune-related adverse events (26). These findings suggest that STING agonists can be activated not only through direct administration but also via alternative mechanisms. Furthermore, their combination with other immunotherapeutic agents, such as PD-1 inhibitors, holds significant promise for cancer treatment by enhancing immune responses in metastatic cancers (27). However, further investigations are essential to optimize delivery systems, clarify mechanistic interactions, and validate these strategies in large-scale clinical trials. An overview of selected STING agonists used in cancer therapy is presented in Table 1.

Table 1: Overview of selected STING agonists in cancer therapy.

STING agonist	Molecular class	Mechanism of action	Development phase	Types of metastatic cancer	Side effects
Cyclic dinucleotides (CDNs) (28)	Nucleotide derivatives (cGAMP, c-di-GMP, c-di-AMP)	Activate STING pathways, stimulating interferon production.	Preclinical and some clinical	Colorectal, breast, and lung cancer	Inflammation, fatigue, headache
Microsphere-based STING agonist (MBOP) (29)	Polymer structures	Activates STING pathways, activating the immune system.	Preclinical	Liver cancer	Immune side effects, injection site reactions
Elumusertib (BAY1895344) (30)	Chemical synthesis	Effectively activates STING pathways.	Phase 1	Prostate cancer	Inflammation, muscle pain
ADU-S100 (22)	Synthesized small molecules	Activates STING, stimulating IFN-I response.	Phase 1/2	Melanoma, lung cancer	High-dose fever, fatigue

This table summarizes key characteristics of various STING agonists currently under investigation for their potential in cancer treatment. It includes information on their molecular class, mechanism of action, current development phase, types of metastatic cancers they are being explored for, and reported side effects.
cGAMP: Cyclic guanosine monophosphate-adenosine monophosphate, c-di-GMP: Cyclic di-guanosine monophosphate , c-di-AMP: Cyclic di-adenosine monophosphate, IFN-I: Interferon type I, STING: Stimulator of interferon genes

Nanoparticle Technology and STING Activation: Structures, Mechanisms, and Clinical Potential

Stimulator of interferon genes agonists have emerged as powerful agents in cancer immunotherapy, particularly in the context of metastatic cancers, where conventional treatments often fall short. However, the clinical utility of these agonists is hindered by pharmacokinetic challenges such as low bioavailability, rapid systemic clearance, and immune-related adverse effects (31). To overcome these limitations, nanoparticle-based drug delivery systems have gained significant attention for their ability to deliver STING agonists effectively to the TME, including metastatic sites (31).

Lipid-Based Nanoparticles and STING Activation in Metastatic Cancer

Lipid-based nanoparticles, particularly liposomes, have been extensively studied for their capacity to enhance the delivery of both hydrophilic and hydrophobic drugs, including STING agonists (32). These nanoparticles are composed of phospholipid bilayers, which can encapsulate a wide range of therapeutic agents, offering protection from degradation and improving stability during circulation (Figure 3) (Supplementary Video 1). In the context of metastatic cancer, where tumor heterogeneity and the presence of distant secondary tumors complicate treatment, the ability of liposomes to deliver STING agonists directly to immune cells within the TME has significant therapeutic implications (32).

The acidic environment characteristic of metastatic tumors, particularly at distant metastatic sites, makes lipid nanoparticles (LNPs) particularly suitable for controlled release (33). These nanoparticles are pH-sensitive, allowing them to release their cargo efficiently within the TME, where the pH (~6.5-6.8) is lower than that of normal tissues (~7.4) (33).

This ensures the STING agonists are released where they are needed the most, potentially enhancing the activation of immune responses at metastatic sites (34).

Lipid-based nanoparticles also have the added benefit of modifying immune responses through their interaction with immune cells (35). These nanoparticles not only deliver STING agonists but also enhance the uptake of the agonists by immune cells, such as dendritic cells and macrophages (36). By triggering the STING pathway, they promote the activation of $CD8^+$ T-cells and the release of pro-inflammatory cytokines, which can lead to a robust anti-tumor immune response (37). In metastatic cancers, where immune evasion is a major hurdle, the ability of lipid-based nanoparticles to stimulate the immune system offers a promising strategy for overcoming this challenge (38).

In addition, surface modifications, such as polyethylene glycol conjugation or antibody conjugation, can improve the specificity of LNPs, enabling them to target specific metastatic tumor cells more effectively (39). These modifications help minimize off-target effects and enhance the accumulation of the nanoparticles at metastatic sites, ensuring that the therapeutic agent is delivered precisely where it is most needed (40).

Studies have demonstrated that lipid-based nanoparticles can successfully deliver STING agonists to immune cells, leading to enhanced antitumor responses in metastatic cancers. For instance, in mouse models of metastatic melanoma and breast cancer, LNPs loaded with STING agonists have been shown to suppress tumor growth and promote the activation of $CD8^+$ T-cells (41). These findings suggest that lipid-based nanoparticles not only act as carriers but also play an active role in modulating immune responses, making them highly suitable for the treatment of metastatic cancers (41).

In conclusion, lipid-based nanoparticles offer a promising approach to overcome the pharmacokinetic challenges associated with STING agonists in the treatment of metastatic cancers. By enhancing the targeted delivery, controlled release, and immune modulation of STING agonists, these nanoparticles hold the potential to improve the efficacy of cancer immunotherapy, particularly in the context of metastatic disease.

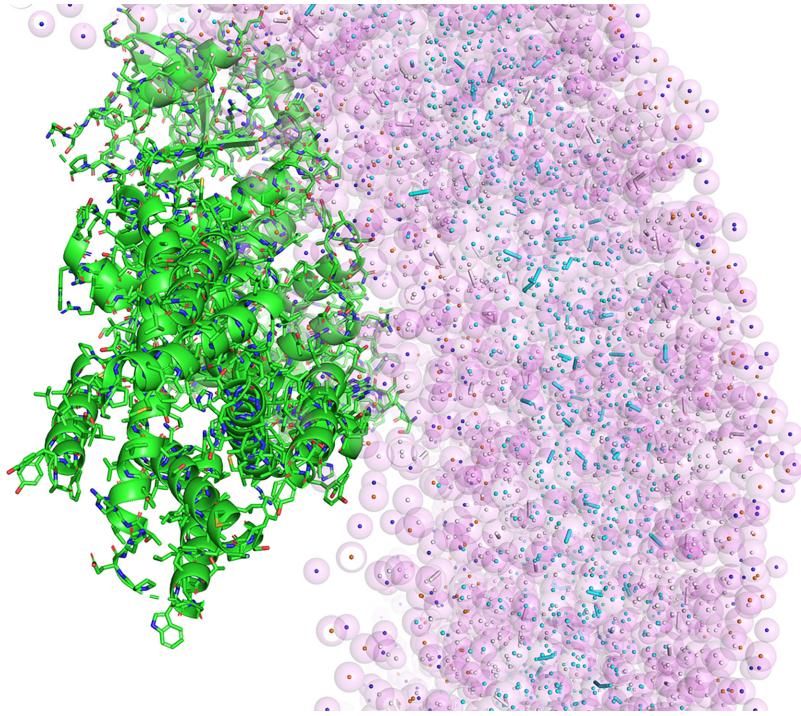


Figure 3: Molecular representation of a liposomal nanoparticle interacting with the STING agonist (with PyMol). The agonist (green) is located at the bilayer interface, demonstrating potential interaction with the synthetic lipid-based nanoparticle model (pink spheres).
STING: Stimulator of interferon genes

Polymer-Based Nanoparticles and STING Activation in Metastatic Cancer Immunotherapy

Polymeric nanoparticles, typically composed of biodegradable polymers such as polylactic-co-glycolic acid (PLGA), are emerging as promising carriers for the delivery of STING agonists in cancer immunotherapy, particularly for metastatic cancers (42). These nanoparticles are well-known for their high drug-loading capacity, controlled release properties, and biocompatibility, making them ideal candidates for overcoming the pharmacokinetic challenges associated with STING agonists (43). When engineered to carry STING agonists, polymer-based nanoparticles ensure that the agonists are efficiently delivered to immune cells, particularly within the TME, where they activate STING receptors and initiate a robust immune response (43).

In the context of metastatic cancer, where tumors are often dispersed across distant sites, the targeted delivery of STING agonists becomes crucial. Polymer nanoparticles can be functionalized with specific ligands or antibodies, enabling them to target particular cells or tissues, including metastatic tumor sites (44). This targeted approach minimizes off-target effects and maximizes the accumulation of the agonists at the site of action, which is especially important for tumors that are hard to treat with conventional therapies (44).

The biodegradable nature of polymer-based nanoparticles allows for the sustained release of STING agonists over an extended period, providing continuous and prolonged activation of immune cells (45). This feature is particularly valuable in metastatic cancers, where immune evasion and immune suppression often hinder the effectiveness of therapies. By ensuring prolonged immune activation, polymer nanoparticles help maintain a strong and persistent antitumor immune response, potentially preventing the re-emergence of metastases (45).

Some studies have demonstrated that polymer-based nanoparticles effectively facilitate the controlled release of STING agonists to immune cells such as dendritic cells, thereby enhancing the activation of $CD8^+$ T-cells and promoting systemic antitumor immunity (46, 47). In metastatic models, this sustained activation has been shown to suppress tumor growth and inhibit the spread of metastatic cells. These characteristics make polymer-based nanoparticles a promising strategy for the long-term, effective modulation of STING activation, offering hope for treating metastatic cancer more effectively than current treatments allow (46, 47).

Inorganic Nanoparticles and STING Activation in Metastatic Cancer Immunotherapy

Inorganic nanoparticles, such as gold (Au), iron oxide (Fe_3O_4), and silica, offer distinct advantages for the treatment of metastatic cancers, including high stability, ease of functionalization, and precise targeting capabilities (48). When STING agonists are incorporated into these nanoparticles, they not only serve as carriers but also enhance antigen transport, facilitate cellular uptake, and modulate immune responses-key factors in overcoming the challenges posed by metastatic tumor dissemination (48).

Magnetic Fe_3O_4 nanoparticles are particularly advantageous for targeting metastatic tumors due to their ability to be guided to specific tumor sites via external magnetic fields (49). This method ensures targeted delivery of STING agonists to distant metastases, improving therapeutic precision and reducing systemic toxicity (49).

Gold nanoparticles, with their photoresponsive properties, can further enhance the therapeutic effect of STING agonists by enabling localized activation upon light exposure (50). This is particularly beneficial for treating deep-seated metastatic tumors, where other methods of delivery may be less effective (50).

Silica nanoparticles, known for their high drug-loading capacity, facilitate the controlled release of STING agonists, ensuring sustained delivery to immune cells such as dendritic cells within the metastatic TME (51). This controlled release is critical in maintaining prolonged immune activation and preventing immune evasion, a common obstacle in metastatic cancers (51).

Recent studies have demonstrated that magnetic Fe_3O_4 nanoparticles can improve STING activation and promote robust antitumor immune responses within metastatic tumors (52). Additionally, Au nanoparticles can optimize the effects of STING agonists through their photoactivatable properties, enhancing their therapeutic potential in the treatment of metastatic cancers (53).

In conclusion, inorganic nanoparticles offer a powerful approach for enhancing the delivery and efficacy of STING agonists in metastatic cancer immunotherapy. With their unique targeting mechanisms, such as magnetic guidance and light activation, these nanoparticles hold great promise for improving the precision and effectiveness of treatment in metastatic disease.

Next-Generation Nanoparticles and STING Activation in Metastatic Cancer Immunotherapy

Innovative smart nanoparticle systems have emerged that involve light-responsive, pH-sensitive, and ligand-targeted nanocarriers, which are promising new modalities to improve STING agonist delivery specificity and efficacy. Much like light-sensitive drugs, light-responsive nanoparticles offer spatiotemporal control for drug release, as they can be activated by illumination either in the TME or even intratumorally, while keeping systemic exposure and the potential for off-target toxicity minimal (54). Photoactivatable nanoparticle platforms are also advantageous for deep-seated tumors or leadership tumors, since controlled and specific activation can be administered chronologically or spatially (55).

pH-sensitive carriers can leverage the acidic environment of the TME or pH sensitivity of endosomes and lysosomes to limit release of STING agonists. This limited release improves the concentration of the drug at the tumor site while avoiding excessive systemic side effects, which are considerable obstacles for clinical translation (56).

Lastly, ligand-targeted nanoparticles, where the nanoparticle scaffold can specifically recognize receptors that are overexpressed on tumor cells or antigen-presenting cells, can direct STING agonists to antigen presenting cells through receptor-mediated uptake and improve biodistribution of the drug. These smart systems can deliver STING agonists to dendritic cells or other immune subsets while improving antigen presentation, T-cell priming, and the overall anti-tumor immune response (57).

Emerging research illustrates the translational potential of these platforms and reports that smart nanocarriers can enhance pharmacokinetic profiles, maintain immune activation, and overcome resistance mechanisms in immunologically "cold" tumors (58). Taken together, these next-generation nanoparticle technologies have considerable clinical development prospects, opening doors for more precise, safer, and more effective STING-based cancer immunotherapies.

2. Evidence from Nanoparticle-Based Preclinical and Clinical Studies

Preclinical and clinical studies have revealed important findings in the evaluation of the potential of nanoparticle-based STING agonist delivery systems in metastatic cancers. For example, in a preclinical study using metal complex lipid-based nanoparticles, targeted delivery of STING agonists to lung cancer cells resulted in significant increases in $CD8^+$ T-cell activity by increasing the release of proinflammatory cytokines such as IFN in the TME. This study demonstrated that nanoparticle-mediated STING activation has the potential to suppress tumor growth by triggering immunogenic cell death mechanisms. However, the lack of long-term in vivo studies and survival data limits the extent to which these findings can be generalized to human applications (59).

Another preclinical study revealed that STING agonist-loaded LNPs can overcome anti-PD-1 resistance through natural killer cell activation. Experiments conducted in a B16-F10 melanoma lung metastasis model demonstrated that STING-LNP treatment induced PD-L1 expression by increasing IFN-γ production, thereby exerting a synergistic antitumor effect with anti-PD-1. These findings indicate that STING-LNPs represent promising candidates for combination therapy in metastatic tumors resistant to anti-PD-1 treatment. Despite these promising results, the translational relevance remains uncertain due to interspecies differences in immune responses and TME factors (38).

In addition, a preclinical study using polymer-based nanoparticles revealed that PLGA nanoparticles provide long-term and controlled release of STING agonists, thus strengthening antitumor immunity by supporting sustainable IFN production in metastatic melanoma (41). Nevertheless, the immunomodulatory capacity of PLGA-based delivery systems requires further optimization, particularly regarding their pharmacokinetics and tumor-targeting specificity in heterogeneous tumor models (43).

Early-stage clinical studies suggest that delivery of STING agonists via lipid-based nanoparticles may enhance immune

response and reduce tumor burden (38). Phase I clinical trials have reported increased IFN-β-mediated immune activation in metastatic lung cancer patients treated with STING agonist-containing nanoparticles but limited treatment responses (36). While some patients have exhibited disease stabilization or partial response, the necessity for further investigation is evident (38).

While these studies support the potential of STING agonist-loaded nanoparticles in the treatment of metastatic cancer, they also demonstrate the need for further research into their clinical efficacy and safety.

3. Challenges and Future Perspectives

While nanoparticle-based delivery of STING agonists holds great promise in preclinical models, tumor-intrinsic resistance mechanisms, along with barriers to clinical translation, interfere with success. Tumors use a variety of mechanisms to inhibit activation of the STING pathway. One well-defined mechanism is hydrolysis of extracellular cGAMP by ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), which limits paracrine immune signaling and dampens anti-tumor immunity via the STING pathway (59). In addition to hydrolysis, TME-mediated epigenetic silencing by transcriptional regulators (e.g., FOXM1) can downregulate cGAS-STING components, reducing cytosolic DNA sensing and IFN-I production (60, 61). Likewise, findings demonstrate that cGAS and STING are often mutated, muscles are missed, or, like TANK-binding kinase 1 and interferon regulatory factor 3 signaling downstream of STING, are deleted or mutated. Furthermore, even non-mutated STING has been shown to lead to immune tolerance with sustained STING activation, which could have a counterproductive effect of impairing antitumor immunity and thus low long-term efficacy of immune pathways (62).

The strong immunostimulatory effects of STING agonists can raise concerns at the clinical level of systemic inflammation, cytokine storm, autoimmunity, and other potential systemic toxicities of prolonged activation. STING agonists, as well as their nanocarrier formulations, could also potentially induce undesired immunogenicity that could activate the innate or adaptive immune pathways differently than intended and result in a decreased therapeutic benefit. There are also challenges that stem from manufacturing issues associated with Good Manufacturing Practice processes, which create additional barriers for reproducibility, scalability, and regulatory approval (58). Treatment is further complicated by the pharmacokinetics of STING agonists and interpatient variation associated with biodistribution of nanoparticles and overall clearance, or circulation half-life, which could create significant variability in therapeutic window and dosing requirements (13). Further concerns include biocompatibility of the nanoparticle formulation, stability, and continued post-marketing biodegradability that require extensive safety assessment in preclinical models and initiating some form of rapid escalating dosing through phase 1 studies (62, 63).

In consideration of such issues, future nanoparticle formulations will aim to provide controlled and local release of STING agonists, limiting systemic side effects while providing better specificity. Smart drug carrier formulations, biodegradable polymers, and multimodal therapeutic formulations with chemotherapy/radiotherapy or checkpoint blockade immunotherapy are some potential strategies to enhance the duration of therapy and overcome resistance (58).

Thus, future research needs to combine approaches for overcoming tumor-intrinsic resistance (i.e., ENPP1 inhibition, epigenetic modulators, or synthetic agonists that could circumvent the inherent signaling deficiencies) with appropriate delivery platforms designed with an eye towards safety, reproducibility, and regulatory approval. Together, they may provide the opportunity for widespread clinical application of STING-based nanomedicines in anti-cancer immunotherapy.

Table 2 highlights important biological and translational obstacles, in addition to potential solutions, for the therapeutic targeting of the STING pathway.

Table 2: Challenges and potential solutions in therapeutic targeting of the STING pathway.

Challenges	Impact	Potential solutions
STING pathway inhibition (development of resistance)	Tumor cells can block STING activation by epigenetic changes or immunosuppressive mechanisms	New generation STING agonists, combination therapy with epigenetic modulators
Development of immune tolerance	Continuous STING activation may lead to tolerance formation and suppression of the immune response	Controlled release nanoparticle systems and dose optimization
Risk of systemic inflammation and autoimmune response	A strong immunostimulatory effect may increase the risk of treatment-related toxicity	Targeted STING activation and biocompatible carrier systems
Biocompatibility, stability, and biodegradability issues of nanoparticles	Needs to be evaluated for long-term safety and efficacy	Smart drug delivery systems, biodegradable polymers
Multimodal treatment requirement	STING activation alone may not be sufficient, combined approaches may be required	Combined treatment strategies with chemotherapy, immunotherapy, and radiotherapy

This table outlines key challenges encountered in developing and applying STING pathway modulators for cancer therapy, along with potential strategies to overcome these obstacles.
STING: Stimulator of interferon genes

CONCLUSION

The STING pathway has emerged as a pivotal target in cancer immunotherapy, particularly in addressing the complex immunosuppressive microenvironment characteristic of metastatic cancers. Despite its therapeutic promise, the clinical application of STING agonists remains hindered by challenges such as low bioavailability, systemic toxicity, and limited tumor specificity when administered directly. To overcome these limitations, nanoparticle-based drug delivery systems have been developed to enable localized, controlled, and sustained activation of the STING pathway within metastatic lesions.

Preclinical and early-phase clinical studies demonstrate that nanoparticle-mediated STING agonist delivery not only amplifies innate and adaptive immune responses but also contributes to the suppression of metastatic tumor growth. Nevertheless, critical challenges persist, including the fine-tuning of dosage, long-term immune regulation, and minimizing off-target immune-related toxicity. Future research should prioritize the engineering of next-generation, biocompatible, and tumor-targeted nanoparticle systems that maximize immunotherapeutic efficacy while minimizing adverse effects.

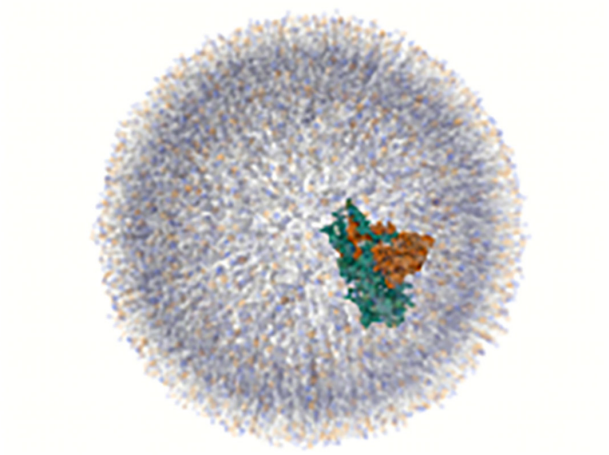
In this context, STING-targeted nanoparticle platforms hold substantial translational potential for the treatment of metastatic cancers. Advancing these technologies through rigorous preclinical validation and well-designed clinical trials will be essential for their integration into standard oncologic practice.

Financial Disclosure: *The author declared that this study received no financial support.*

REFERENCES

1. World Health Organization. (2020). Cancer. [Crossref]
2. Kilmister EJ, Koh SP, Weth FR et al. Cancer metastasis and treatment resistance: mechanistic insights and therapeutic targeting of cancer stem cells and the tumor microenvironment. Biomedicines. 2022;10(11):2988. [Crossref]
3. Kim SK, Cho SW. The evasion mechanisms of cancer immunity and drug intervention in the tumor microenvironment. Front Pharmacol. 2022;13:868695. [Crossref]
4. Cao LL, Kagan JC. Targeting innate immune pathways for cancer immunotherapy. Immunity. 2023;56(10):2206-17. [Crossref]
5. Huang R, Ning Q, Zhao J et al. Targeting STING for cancer immunotherapy: from mechanisms to translation. Int Immunopharmacol. 2022;113(Pt A):109304. [Crossref]
6. Ishikawa H, Barber GN. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature. 2008;455(7213):674-8. [Crossref]
7. Corrales L, Glickman LH, McWhirter SM et al. Direct activation of STING in the tumor microenvironment leads to potent and systemic tumor regression and immunity. Cell Rep. 2015;11(7):1018-30. [Crossref]
8. Sivick KE, Desbien AL, Glickman LH et al. Magnitude of therapeutic STING activation determines CD8+ T-cell-mediated anti-tumor immunity. Cell Rep. 2018;25(11):3074-85.e5. [Crossref]
9. Li J, Duran MA, Dhanota N et al. Metastasis and immune evasion from extracellular cGAMP hydrolysis. Cancer Discov. 2021;11(5):1212-27. [Crossref]
10. Hines JB, Kacew AJ, Sweis RF. The development of STING agonists and emerging results as a cancer immunotherapy. Curr Oncol Rep. 2023;25(3):189-99. [Crossref]
11. Wang F, Su H, Xu D et al. Tumour sensitization via the extended intratumoural release of a STING agonist and camptothecin from a self-assembled hydrogel. Nat Biomed Eng. 2020;4(11):1090-101. [Crossref]
12. Manzari-Tavakoli A, Babajani A, Tavakoli MM et al. Integrating natural compounds and nanoparticle-based drug delivery systems: a novel strategy for enhanced efficacy and selectivity in cancer therapy. Cancer Med. 2024;13(5):e7010. [Crossref]
13. Chen X, Xu Z, Li T et al. Nanomaterial-encapsulated STING agonists for immune modulation in cancer therapy. Biomark Res. 2024;12(1):2. [Crossref]
14. Florian DC, Bennett NE, Odziomek M et al. Nanoparticle STING agonist reprograms the bone marrow to an antitumor phenotype and protects against bone destruction. Cancer Res Commun. 2023;3(2):223-34. [Crossref]
15. Shirley CA, Chhabra G, Amiri D et al. Immune escape and metastasis mechanisms in melanoma: breaking down the dichotomy. Front Immunol. 2024;15:1336023. [Crossref]
16. National Cancer Institute. (2020, March 6). Mapping cancer genomic evolution offers insights into tumor development. Cancer Currents Blog.[Crossref]
17. Lozac'hmeur A, Danek T, Yang Q et al. Detecting HLA loss of heterozygosity within a standard diagnostic sequencing workflow for prognostic and therapeutic opportunities. NPJ Precis Oncol. 2024;8(1):174. [Crossref]
18. Wang Z, Cao YJ. Adoptive cell therapy targeting neoantigens: a frontier for cancer research. Front Immunol. 2020;11:176. [Crossref]
19. Zhu Y, An X, Zhang X et al. STING: a master regulator in the cancer-immunity cycle. Mol Cancer. 2019;18(1):152. [Crossref]
20. Amouzegar A, Chelvanambi M, Filderman JN et al. STING agonists as cancer therapeutics. Cancers (Basel). 2021;13(11):2695. [Crossref]
21. Shen M, Jiang X, Peng Q et al. The cGAS–STING pathway in cancer immunity: mechanisms, challenges, and therapeutic implications. J Hematol Oncol. 2025;18(1):40. Erratum in: J Hematol Oncol. 2025;18(1):49. [Crossref]
22. Meric-Bernstam F, Sweis RF, Hodi FS et al. Phase I dose-escalation trial of MIW815 (ADU-S100), an intratumoral STING agonist, in patients with advanced/metastatic solid tumors or lymphomas. Clin Cancer Res. 2022;28(4):677-88. [Crossref]
23. Bartusik-Aebisher D, Rogóż K, Aebisher D. STING-activating nanoparticles combined with PD-1/PD-L1 blockade: a synergistic approach in cancer immunotherapy. Biomedicines. 2025;13(9):2160. [Crossref]
24. Huang M, Cha Z, Liu R et al. Enhancing immunotherapy outcomes by targeted remodeling of the tumor microenvironment via combined cGAS-STING pathway strategies. Front Immunol. 2024;15:1399926. [Crossref]
25. Li RF, Liu S, Gao Q et al. Inhibition of CDH11 activates cGAS-STING by Stimulating branched chain amino acid catabolism and mitigates lung metastasis of adenoid cystic carcinoma. Adv Sci (Weinh). 2025;12(8):e2408751. [Crossref]
26. Ghaffari A, Peterson N, Khalaj K et al. STING agonist therapy in combination with PD-1 immune checkpoint blockade enhances response to carboplatin chemotherapy in high-grade serous ovarian cancer. Br J Cancer. 2018;119(4):440-9. [Crossref]
27. Vasiyani H, Wadhwa B, Singh R. Regulation of cGAS-STING signalling in cancer: approach for combination therapy. Biochim Biophys Acta Rev Cancer. 2023;1878(3):188896. [Crossref]
28. Dejmek M, Brazdova A, Otava T et al. Vinylphosphonate-based cyclic dinucleotides enhance STING-mediated cancer immunotherapy. Eur J Med Chem. 2023;259:115685. [Crossref]
29. Watkins-Schulz R, Tiet P, Gallovic MD et al. A microparticle platform for STING-targeted immunotherapy enhances natural killer cell- and CD8+ T-cell-mediated anti-tumor immunity. Biomaterials. 2019;205:94-105. [Crossref]
30. Yap TA, Tan DSP, Terbuch A et al. First-in-human trial of the oral ataxia telangiectasia and RAD3-related (ATR) inhibitor BAY 1895344 in patients with advanced solid tumors. Cancer Discov. 2021;11(1):80-91. [Crossref]
31. Chen S, Peng A, Chen M et al. Nanomedicines targeting activation of STING to reshape tumor immune microenvironment and enhance immunotherapeutic efficacy. Front Oncol. 2023;12:1093240. [Crossref]
32. Shaji SG, Patel P, Mamani UF et al. Delivery of a STING agonist using lipid nanoparticles inhibits pancreatic cancer growth. Int J Nanomedicine. 2024;19:8769-78. [Crossref]
33. Yan Y, Ding H. pH-responsive nanoparticles for cancer immunotherapy: a brief review. Nanomaterials (Basel). 2020;10(8):1613. [Crossref]
34. He Y, Zheng K, Qin X et al. Intravenous delivery of STING agonists using acid-sensitive polycationic polymer-modified lipid nanoparticles for enhanced tumor immunotherapy. Acta Pharm Sin B. 2025;15(3):1211-29. [Crossref]

35. Connors J, Joyner D, Mege NJ et al. Lipid nanoparticles (LNP) induce activation and maturation of antigen presenting cells in young and aged individuals. Commun Biol. 2023;6(1):188. [Crossref]
36. Sun X, Huang X, Park KS et al. Self-assembled STING-activating coordination nanoparticles for cancer immunotherapy and vaccine applications. ACS Nano. 2024;18(15):10439-53. [Crossref]
37. Li W, Lu L, Lu J et al. cGAS-STING-mediated DNA sensing maintains CD8+ T-cell stemness and promotes antitumor T-cell therapy. Sci Transl Med. 2020;12(549):eaay9013. [Crossref]
38. Nakamura T, Sato T, Endo R et al. STING agonist loaded lipid nanoparticles overcome anti-PD-1 resistance in melanoma lung metastasis via NK cell activation. J Immunother Cancer. 2021;9(7):e002852. [Crossref]
39. Anwar DM, Hedeya HY, Ghozlan SH et al. Surface-modified lipid-based nanocarriers as a pivotal delivery approach for cancer therapy: application and recent advances in targeted cancer treatment. Beni-Suef Univ J Basic Appl Sci. 2024;13:106. [Crossref]
40. Shi J, Kantoff PW, Wooster R et al. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer. 2017;17(1):20-37. [Crossref]
41. Zhang J, Cui X, Huang Y et al. Anticancer effect of STING agonist-encapsulated liposomes on breast cancer. Molecules. 2023;28(9):3740. [Crossref]
42. Podojil JR, Cogswell AC, Chiang MY et al. Biodegradable nanoparticles induce cGAS/STING-dependent reprogramming of myeloid cells to promote tumor immunotherapy. Front Immunol. 2022;13:887649. [Crossref]
43. Lu X, Miao L, Gao W et al. Engineered PLGA microparticles for long-term, pulsatile release of STING agonist for cancer immunotherapy. Sci Transl Med. 2020;12(556):eaaz6606. [Crossref]
44. Marques AC, Costa PJ, Velho S et al. Functionalizing nanoparticles with cancer-targeting antibodies: a comparison of strategies. J Control Release. 2020;320:180-200. [Crossref]
45. Qiao Y, Wei L, Su Y et al. Nanoparticle-based strategies to enhance the efficacy of sting activators in cancer immunotherapy. Int J Nanomedicine. 2025;20:5429-56. [Crossref]
46. Li Y, Yi J, Ma R et al. A polymeric nanoplatform enhances the cGAS-STING pathway in macrophages to potentiate phagocytosis for cancer immunotherapy. J Control Release. 2024;373:447-62. [Crossref]
47. Covarrubias G, Moon TJ, Loutrianakis G et al. Comparison of the uptake of untargeted and targeted immunostimulatory nanoparticles by immune cells in the microenvironment of metastatic breast cancer. J Mater Chem B. 2022;10(2):224-35. [Crossref]
48. Sun Z, Wang Z, Wang T et al. Biodegradable MnO-based nanoparticles with engineering surface for tumor therapy: simultaneous fenton-like ion delivery and immune activation. ACS Nano. 2022;16(8):11862-75. [Crossref]
49. Chen F, Li T, Zhang H et al. Acid-ionizable iron nanoadjuvant augments sting activation for personalized vaccination immunotherapy of cancer. Adv Mater. 2023;35(10):e2209910. [Crossref]
50. Fang K, Zhang H, Kong Q et al. Recent progress in photothermal, photodynamic and sonodynamic cancer therapy: through the cgas-sting pathway to efficacy-enhancing strategies. Molecules. 2024;29(15):3704. [Crossref]
51. Chen YP, Xu L, Tang TW et al. STING activator c-di-GMP-loaded mesoporous silica nanoparticles enhance immunotherapy against breast cancer. ACS Appl Mater Interfaces. 2020;12(51):56741-52. [Crossref]
52. Li T, Song R, Sun F et al. Bioinspired magnetic nanocomplexes amplifying STING activation of tumor-associated macrophages to potentiate cancer immunotherapy. Nano Today. 2022;43:101400.[Crossref]
53. Lu D, Li W, Tan J et al. STING agonist delivered by neutrophil membrane-coated gold nanoparticles exerts synergistic tumor inhibition with radiotherapy. ACS Appl Mater Interfaces. 2024;16(40):53474-88. [Crossref]
54. Almadani IF, Almadani MF, AlSawaftah N et al. Nanocarriers Responsive to Light—A Review. Micro. 2024; 4(4):827-44. [Crossref]
55. Lee S, Kim S, Kim D et al. Spatiotemporally controlled drug delivery via photothermally driven conformational change of self-integrated plasmonic hybrid nanogels. J Nanobiotechnology. 2023;21(1):191. [Crossref]
56. Lu X, Xia H, Gao W et al. A pH-responsive and guanidinium-rich nanoadjuvant efficiently delivers sting agonist for cancer immunotherapy. ACS Nano. 2025;19(7):6758-70. [Crossref]
57. Doshi AS, Cantin S, Prickett LB et al. Systemic nano-delivery of low-dose STING agonist targeted to CD103+ dendritic cells for cancer immunotherapy. J Control Release. 2022;345:721-33. [Crossref]
58. Ying X, Chen Q, Yang Y et al. Nanomedicines harnessing cGAS-STING pathway: sparking immune revitalization to transform 'cold' tumors into 'hot' tumors. Mol Cancer. 2024;23(1):277. [Crossref]
59. Khalifa AM, Nakamura T, Sato Y et al. Vaccination with a combination of STING agonist-loaded lipid nanoparticles and CpG-ODNs protects against lung metastasis via the induction of $CD11b^{high}$ $CD27^{low}$ memory-like NK cells. Exp Hematol Oncol. 2024;13(1):36. [Crossref]
60. Timilsina S, Huang JY, Abdelfattah N et al. Epigenetic silencing of DNA sensing pathway by FOXM1 blocks stress ligand-dependent antitumor immunity and immune memory. Nat Commun. 2025;16(1):3967.[Crossref]
61. Zheng H, Wu L, Xiao Q et al. Epigenetically suppressed tumor cell intrinsic STING promotes tumor immune escape. Biomed Pharmacother. 2023;157:114033. [Crossref]
62. Yue B, Gao W, Lovell JF et al. The cGAS-STING pathway in cancer immunity: dual roles, therapeutic strategies, and clinical challenges. Essays Biochem. 2025;69(2):EBC20253006. [Crossref]
63. Dobrovolskaia MA. Pre-clinical immunotoxicity studies of nanotechnology-formulated drugs: challenges, considerations and strategy. J Control Release. 2015;220(Pt B):571-83. [Crossref]



Supplementary Video 1: 3D animation showing the docking of a STING agonist with a liposomal nanoparticle. The animation demonstrates the spatial orientation and interaction interface between the STING agonist and the liposome surface. The molecular structures were visualized using Mol* after molecular docking (with HDOCK), and the dynamic rotation highlights the predicted binding region.
3D: Three-dimentional, STING: Stimulator of interferon genes