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Agonists Targeting the cGAS-STING Signaling Pathway and Their Applications in Cancer Therapy

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Abstract

The cyclic GMP-AMP synthase (cGAS) serves as a pivotal component of the immune system, playing a crucial role in regulating the innate immune response elicited by both exogenous and endogenous DNA. This enzyme recognizes the aberrant presence of DNA in the cytoplasm, subsequently activating the signaling pathway mediated by the stimulator of interferon genes (STING) and thereby fulfilling a critical role in immune response mechanisms. This review delineates the mechanisms of the cGAS-STING pathway and elucidates the small-molecule agonists targeting STING, along with their combined applications in various tumor treatment strategies. The aim of this review is to provide a valuable reference framework and insights for ongoing research in related fields.

Keywords: cGAS-STING, signaling pathway, agonists, combined therapy

1. Introduction

Malignant tumors represent a significant threat to human health. Currently, traditional treatment modalities, including surgical resection, radiotherapy, and chemotherapy, continue to be the predominant approaches in cancer treatment strategies. In recent years, immunotherapy has progressively emerged as an alternative strategy for cancer treatment. Generally, chemotherapy eliminates cancer cells via direct cytotoxic effects; however, it frequently faces challenges related to drug resistance and adverse side effects. In contrast, immunotherapy seeks to modulate immune responses by either activating the immune defense system or reshaping the tumor microenvironment. Furthermore, many chemotherapeutic agents can induce DNA damage within cells, potentially initiating innate immune responses that target and eliminate cancer cells. As a crucial component of the innate immune mechanism, the cGAS-STING signaling pathway plays a pivotal role in recognizing aberrant DNA within tumor cells and triggering immune responses. Activation of this pathway can trigger the release of interferons and various pro-inflammatory cytokines, thereby enhancing immune surveillance within the tumor microenvironment and effectively inhibiting tumor growth and metastasis.

2. cGAS-STING Pathway

The cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS) serves as an intracellular sensor in the innate immune system, recognizing double-stranded DNA (dsDNA). cGAS can detect both exogenous dsDNA derived from bacteria, DNA viruses, and retroviruses, as well as endogenous dsDNA, including mitochondrial DNA released during apoptosis and chromatin fragments generated from chromosomal replication errors. This recognition process subsequently triggers the host's defense mechanisms. Upon binding to DNA molecules, cGAS forms a complex that catalyzes the conversion of ATP and GTP into the signaling molecule cyclic guanosine monophosphate-adenosine monophosphate (cGAMP). As a second messenger, cGAMP activates the stimulator of interferon genes (STING) protein located in the endoplasmic reticulum by binding to its C-terminal. This interaction promotes the transport of STING to the Golgi apparatus through higher-order oligomerization and tetramer formation. Subsequently, STING undergoes palmitoylation, inducing conformational changes and oligomerization that lead to the recruitment of TANK-binding kinase 1 (TBK1) and IκB kinases (IKK). These kinases subsequently undergo autophosphorylation. The phosphorylated forms of TBK1 and IKK can activate critical transcriptional regulators, specifically interferon regulatory factor 3 (IRF3) and nuclear factor kappa-B (NF-κB). This activation process subsequently induces the expression of a range of pro-inflammatory cytokines, including type I interferons (IFN-I), interleukin-6 (IL-6), and tumor necrosis factor (TNF). The release of these cytokines plays a crucial role in triggering immune responses that inhibit and even eliminate cancer cells.

3. STING Agonists

Activation of the STING signaling pathway significantly enhances the downstream response mechanisms of type I interferons (IFN-I), which play a critical role in tumor immune responses. Current research efforts focus on the development of agonists targeting STING to explore their potential applications in cancer therapy. These agonists are primarily categorized into two classes: cyclic dinucleotides (CDNs) and non-cyclic dinucleotides (non-CDNs) small molecule agonists. Both classes of agonists are considered key strategies for activating the STING pathway and subsequently promoting anti-tumor immune responses. The development of these compounds is of significant importance for advancing the field of cancer immunotherapy.

3.1 Cyclic Dinucleotides

Cyclic dinucleotides (CDNs) represent a class of compounds that include molecules such as cyclic di-GMP (c-di-GMP), cyclic di-AMP (c-di-AMP), and cyclic GMP-AMP (cGAMP). Among these, cGAMP exists in several structural forms, including 2',3'-cGAMP, 3',3'-cGAMP, 2',5'-cGAMP, and 3',5'-cGAMP. In mammals, 2',3'-cGAMP is the only known cyclic dinucleotide synthesized by the cGAS enzyme. Endogenous STING agonists, including 2',3'-cGAMP and 3',3'-cGAMP, encounter several challenges, such as insufficient in vivo efficacy, rapid metabolic clearance, and low response rates in clinical trials. Consequently, chemical modifications of these agonists aimed at enhancing their stability and therapeutic efficacy have gained particular importance.

3.2 Non-CDNs

diABZI was first identified as a non-cyclic dinucleotide (non-CDN) STING agonist, exhibiting a strong affinity for the human STING protein and demonstrating significant systemic therapeutic effects in the treatment of murine tumors. Researchers identified amidobenzimidazole (ABZI) compounds through high-throughput screening, which bind specifically to the cGAMP binding pocket, with each molecule interacting with an individual STING subunit (Ramanjulu et al., 2018). Leveraging the symmetry of the STING protein, the researchers developed a linking strategy that enabled two symmetrically related ABZI compounds to produce a synergistic effect, resulting in the creation of linked ABZIs (diABZIs) that enhance STING binding and cellular function. Subsequently, a single diABZI was administered intravenously to immunocompetent mice bearing established syngeneic colon cancer, triggering robust antitumor activity and resulting in complete and durable tumor regression.

4. Combined Use of STING Agonists and Tumor Therapies

4.1 STING Agonists and Traditional Therapies

Gold nanoparticles represent a promising class of radiosensitizers. Researchers covalently linked gold nanoparticles to the STING agonist MSA-2 (MSA-Au) and combined them with cRGD-modified neutrophil membranes to create M-Au@RGD-NM. Following combined radiotherapy, tumor-bearing mice exhibited significant tumor suppression. M-Au@RGD-NM significantly activated the STING pathway and modulated systemic immune responses. In vivo dynamic imaging demonstrated its preferential targeting of tumors following radiotherapy (Lu et al., 2024). 5-Fluorouracil, a widely utilized anticancer drug, exerts its therapeutic effects primarily by inhibiting DNA synthesis; however, it is associated with significant side effects. However, when administered in conjunction with 2',3'-cGAMP, its antitumor efficacy was enhanced in a colorectal cancer mouse model, while toxic side effects were also mitigated (Li et al., 2016).

4.2 STING Agonists and Immune Checkpoint Inhibitors

In TC-1 and U14 cervical cancer mouse models, the STING agonist MSA-2, administered either as monotherapy or in conjunction with anti-PD-1 therapy, effectively suppressed subcutaneous cervical tumor growth; notably, the combination treatment resulted in significantly enhanced outcomes, prolonging mouse survival, augmenting the presence of $CD3^+$ and $CD8^+$ T cells within the tumor microenvironment, and facilitating tumor cell apoptosis (Li T et al., 2024). In a liver metastasis model, intramuscular injection of the STING agonist BMS-986301, in combination with the anti-PD-1 antibody, significantly prolonged mouse survival and demonstrated inhibitory effects on distant subcutaneous tumors. In a genetically engineered KPC mouse model that spontaneously develops pancreatic ductal adenocarcinoma (PDAC), intramuscular injection of BMS-986301, in conjunction with anti-CTLA-4 and anti-PD-1 antibodies, significantly extended mouse survival. In human tumor xenograft models, both intratumoral and intramuscular administrations of BMS-986301 effectively inhibited tumor growth (Li K et al., 2024).

4.3 STING Agonists and Tumor Vaccines

STINGVAX is a tumor vaccine formulated with CDNs and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Fu et al., 2015). In vivo experiments conducted across various cancer models demonstrated that

STINGVAX exhibited significantly enhanced antitumor efficacy compared to the GM-CSF-containing tumor cell vaccine GM-vac, which lacks a STING agonist. Furthermore, the combination of STINGVAX with PD-1 antibodies was shown to further amplify the antitumor response and promote tumor regression. In a metastatic breast cancer mouse model, immunization with a live-attenuated Listeria monocytogenes vaccine expressing the tumor-associated antigen Mage-b, in conjunction with a high dose of the STING agonist c-di-GMP, resulted in complete tumor clearance in the mice; neither c-di-GMP nor LM-Mb alone achieved this outcome (Chandra et al., 2014). Additionally, in a subcutaneous B16 melanoma mouse model, c-di-GMP enhanced the immunogenicity and antitumor effects of the peptide vaccine TriVax, leading to the induction of a significant number of antigen-specific $CD8^+$ T cells that recognized and inhibited melanoma cell growth (Wang et al., 2015).

4.4 STING Agonists and T Cell Therapy

Research has demonstrated that in the orthotopic model of locally advanced breast cancer, the combined application of STING agonists, such as DMXAA or cGAMP, enhances the proliferation and infiltration of Th/Tc17 CAR-T cells at the tumor site, thereby reducing tumor growth (Xu et al., 2021). CAR-T therapy encounters limitations in the treatment of solid tumors; one strategy to overcome this challenge is to combine it with agents that modulate the tumor immune microenvironment. IMSA101, a novel cGAMP analog and STING agonist, demonstrates superior stability in human serum relative to cGAMP. In two syngeneic tumor models, specifically PDA7940b pancreatic cancer and B16-huCD19 melanoma, the combination of IMSA101 with CAR-T therapy significantly improved the overall survival rates of the mice, with complete tumor remission observed in some subjects. Treatment with IMSA101 increased the infiltration of CAR-T cells as well as other immune cells, including macrophages, neutrophils, and NK cells, into the tumor while reducing the number of regulatory T cells. Pathological evaluation revealed an increase in necrosis and inflammatory markers within the tumors (Uslu et al., 2024).

4.5 STING Agonists and Other Therapies

In addition to the previously mentioned combination therapies, numerous reports exist regarding the use of STING agonists in conjunction with other modalities for tumor treatment. VPS34 is a critical protein in the autophagy process, and SB02024, a VPS34 inhibitor, suppresses autophagy, thereby facilitating the activation of cGAS by STING agonists. In a B16F10 melanoma mouse model, the combination of SB02024 and the STING agonist ADU-S100 significantly reduced tumor growth and markedly extended survival compared to monotherapy (Bartolini et al., 2024). In mouse models of B16F10 melanoma and 4T1 breast cancer, the STING agonist cGAMP, in combination with the anti-vascular peptide RGD-(KLAKLAK)2, enhanced the destruction of tumor vasculature while also activating innate immune responses, thereby improving anticancer efficacy (Czapla et al., 2024).

5. Conclusions

In the context of innate immunity, the cGAS-STING pathway recognizes cytoplasmic DNA, regulates macrophage polarization, and activates DCs. In adaptive immunity, the activation of this pathway can promote $CD8^+$ T cell proliferation, regulate $CD4^+$ T cell differentiation, and enhance antibody production. Although the signaling mechanisms of the cGAS-STING pathway in tumors remain not fully understood, the combination of STING agonists with various cancer therapies has demonstrated significant synergistic anticancer effects in several preclinical tumor models. These agonists not only effectively alleviate the burden of chemotherapy side effects but also address the challenges of treatment resistance, leading to marked improvements in therapeutic outcomes and injecting new vitality into the development of novel anticancer treatment strategies. Nevertheless, the specific molecular mechanisms underlying this synergistic effect remain under investigation, and further detailed studies are required to enhance our understanding of the role of STING in the tumor microenvironment and its regulation of immune responses at the mechanistic level.

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