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Research Progress of cGAS STING Pathway in Tumor Therapy

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Abstract: The cGAS-STING pathway's activation and regulatory mechanisms, as well as its possible involvement in carcinogenesis and cancer treatment, are explored in this article. As a crucial pattern recognition receptor, cGAS may recognize aberrant cytosolic double-stranded DNA, catalyze the synthesis of cGAMP, and activate the STING protein, which is located in the endoplasmic reticulum. This activation causes type I interferons to be secreted, transcription factors such IRF3 to be inducted, and inflammatory reactions that impact cell division and death. Because this route is continuously activated in the tumor microenvironment, it can promote tumor cell proliferation and immune surveillance evasion while also having anti-tumor actions and the potential to cause chronic inflammation. Additionally, the cGAS-STING pathway can produce a number of pro-inflammatory molecules that help immune cells destroy malignancies. Small chemical agonists that target the cGAS-STING pathway are currently being developed with encouraging results, and combined therapeutic approaches have showed promise. Future research is expected to further expand the application of cGAS-STING pathway activators in more types of tumors and in combination with other therapeutic approaches, bringing new hope for cancer patients. At the same time, we must be vigilant about the connection between abnormal activation of the cGAS-STING pathway and autoimmune diseases to ensure the safety and efficacy of treatments.

Keywords: cGAS STING pathway, anti-tumor, immunotherapy

1. Introduction

A crucial pattern recognition receptor called cyclic guanosine monophosphate adenosine monophosphate synthase (cGAS) can identify double stranded DNA (dsDNA) that manifests aberrantly in the cytoplasm. When cGAS is activated, it uses adenosine triphosphate (ATP) and guanosine triphosphate (GTP) as substrates to catalyze the production of cyclic guanosine monophosphate adenosine monophosphate (cGAMP), a special second messenger[1]. A transmembrane protein found in the endoplasmic reticulum, stimulator of interferon genes (STING) is a crucial linker molecule downstream in the cGAS pathway. When STING binds to cGAMP, it oligomerizes and moves from the endoplasmic reticulum to inner membrane organelles like the Golgi apparatus, activating STING. By recruiting and activating downstream protein kinases, this mechanism further increases STING, which in turn activates transcription factors including interferon

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regulatory factor 3 (IRF3) and other signaling factors[2]. This activation initiates inflammatory responses, inhibits cell proliferation and apoptosis, and is thus crucial in anti-tumor innate immunity.

The cGAS STING pathway is activated in the tumor microenvironment when a significant amount of tumor-derived DNA is released into the cytoplasm as a result of the tumor cells' fast growth, necrosis, and genomic instability. This pathway's activation encourages the synthesis of inflammatory factors and draws in immune cell infiltration[3], It makes it easier for the immune system to identify and get rid of cancerous cells. To activate immune cells like cytotoxic T lymphocytes to destroy tumor cells, the cGAS STING pathway, on the one hand, improves the ability of antigen-presenting cells like dendritic cells to absorb, digest, and present tumor-associated antigens[4]; On the other hand, this pathway can also directly target on tumor cells, inducing apoptosis and inhibiting their growth and metastasis.

2. Activation and regulatory mechanisms of cGAS STING pathway

2.1. Formation of cGAMP

CGAS identifies dsDNA through its DNA-binding sites and a zinc envelope structure, which is contingent upon its ability to recognize the phosphate-ribose backbone structure[5]. The DNA-binding domain of cGAS possesses a positive charge surface, enabling it to engage in electrostatic interactions with the negatively charged phosphate backbone of DNA. In addition, specific domains within cGAS are capable of aligning with and binding to the double helix structure of DNA, achieving specific recognition of DNA. At the mechanistic level, cGAS recognizes dsDNA based on DNA length rather than sequence[6]. Extended dsDNA segments are more effective in promoting CGAS dimerization, which in turn, more potently activates CGAS.

Upon encountering and binding to DNA within the cytoplasm, CGAS undergoes a series of conformational changes that activate its NTase domain[7]. In this activated state, GTP and ATP are precisely located to participate in the reaction. Subsequently, cGAS rearranges and connects the phosphate groups of GTP and ATP through a series of phosphate transfer reactions, forming cGAMP. This process involves the cleavage and formation of chemical bonds, specifically the formation of a 2'-5' phosphodiester bond and a 3'-5' phosphodiester bond between guanylate and adenylate[8], resulting in the formation of cGAMP with a unique cyclic structure.

2.2. Activation and Transport of STING Proteins

After binding to cGAMP, the STING protein undergoes a critical dimerization process. This dimer formation of dimers is a critical step in the activation process, leading to conformational changes in STING that enhance its interaction with downstream signaling molecules[9]. As shown in Figure 1 the cGAMP-activated STING protein needs to be transported from the endoplasmic reticulum (ER) to the Golgi complex to continue the signaling process. Initially, the activated STING protein engages with ER-associated transport vesicles, including coat protein II (COP II) complex[10]. COP II protein can recognize and encapsulate STING protein, forming transport vesicles. These vesicles detach from the endoplasmic reticulum and begin transporting STING proteins towards the Golgi complex[11].

Throughout this transport, vesicles navigate along microtubule tracks towards the Golgi complex under the traction of molecular motor proteins. When the vesicle reaches the Golgi complex, the vesicle membrane fuses with the membrane of the Golgi complex, thereby releasing STING into the Golgi apparatus to continue its role in the signaling pathway.

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2.3. Pathway activation to type I interferon secretion

Activated STING dimers can recruit TANK binding kinase 1 (TBK1)[12]. When the STING dimer interacts with TBK1, a serine/threonine protein kinase, it becomes active. The structure of TBK1's activation loop, an area for kinase activity, changes conformationally as a result of this interaction. The structural change makes it easier for TBK1 to bind and use ATP. ATP, as a donor of phosphate groups, transfers phosphate groups to serine and threonine residues under the catalysis of TBK1, thereby achieving phosphorylation of TBK1[13].

Phosphorylated TBK1 subsequently recognizes and binds to specific structural domains of IRF3, phosphorylating it in the process. The phosphorylation mainly targets the C-terminal region of IRF3, which contains multiple serine and threonine residues, thereby activating IRF3. Once phosphorylated, IRF3 undergoes conformational changes, causing multiple phosphorylated IRF3 molecules to form dimers[14]. Dimerization exposes the nuclear localization sequence (NLS) within the IRF3 molecule.

Through the nuclear pore complex, the IRF3 dimer moves to the nucleus with its NLS exposed. IRF3 dimer binds to the promoter area of type I interferon genes like IFN-α and IFN-β in the nucleus and works with other transcription factors like NF-κB[15]. This combination initiates the transcription process of type I interferon genes, promoting cells tp synthesize and secrete of type I interferon. These interferons then act on neighboring cells, triggering antiviral and immune regulatory signaling pathways.

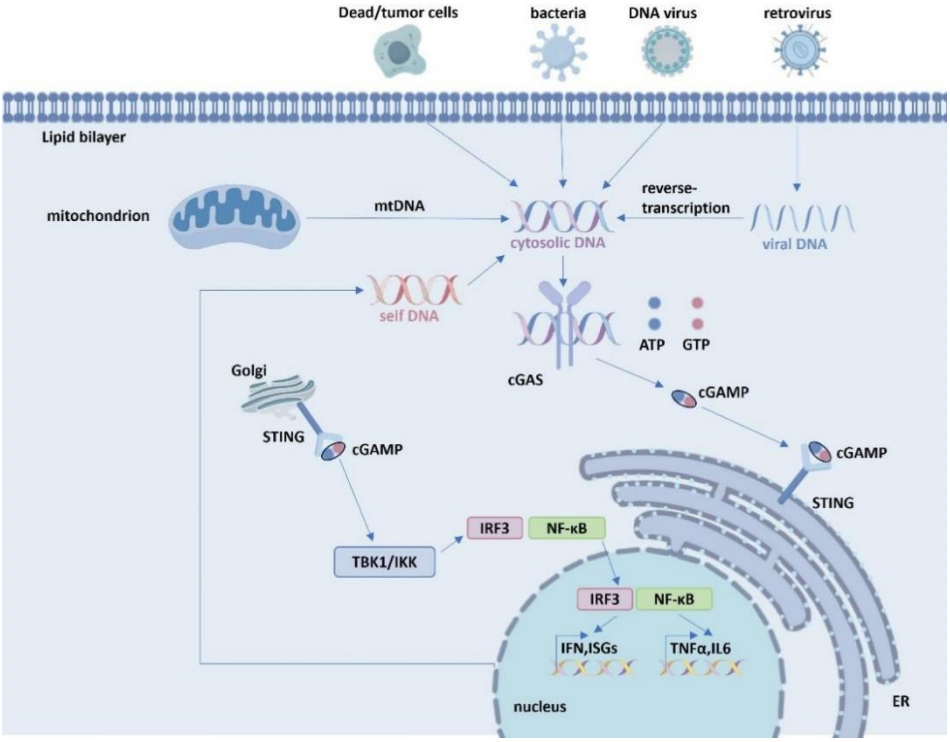

Figure 1: Activation of cGAS STING pathway

3. The association between cGAS STING pathway and tumorigenesis

3.1. Anti tumor and pro tumor effects

In the context the process of chromosomal instability within cancer cells, DNA damage occurs, which allows DNA fragments to escape into the cytoplasm and subsequently activate the cGAS STING signaling path[16]. The body's capacity to eliminate tumor cells is improved when this signaling

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pathway is activated because it increases the transcription of type I interferon genes, which activates immune cells and stimulates the expression of other immune-related genes. Furthermore, cGAS STING pathway activation can increase the effectiveness of cyclin-dependent kinase inhibitors, causing tumor cells to arrest in the G1 or G2/M phase and so halting their growth[17]. It is worth noting that the cGAS STING pathway has also been found to promote tumor vascular remodeling, improve the tumor microenvironment, enhance immune cell infiltration and drug delivery efficiency. These effects collectively augment the potency of anti-tumor immunotherapies[18].

However, chronic inflammatory states can result from sustained activation of the cGAS-STING signaling pathway, which releases a variety of inflammatory mediators that may have negative effects on tumor formation in addition to promoting tumor cell migration, survival, and proliferation. Chronic inflammation can further recruit immunosuppressive cells, which suppress the activity of immune cells through various mechanisms and assist tumor cells in evading immune system surveillance. Through certain processes, some tumor cells may become resistant to the cGAS STING pathway during tumor formation. This might result in the pathway being activated continuously and producing signals that are advantageous for the survival of tumor cells[19]. This complex interaction suggests that the long-term effects of cGAS-STING pathway activation on the tumor microenvironment and immune response must be carefully considered when developing anti-cancer treatments targeting this system.

3.2. Production of pro-inflammatory cytokines

The cGAS-STING pathway triggers a series of immunological reactions when it detects dsDNA from tumor origins. The transcription factor IRF3 is first phosphorylated by TBK1, which is first engaged and activated by this route. After dimerizing and migrating to the nucleus, phosphorylated IRF3 works with other transcription factors to trigger the transcription of the type I interferon gene[20]. Type I interferon can recruit and activate natural killer (NK) cells. NK cells are activated to release perforin and granzyme, activating the apoptotic pathway and inducing tumor cell apoptosis[21]. In addition, type I interferon can effectively promote the maturation of dendritic cells (DCs), enhance their antigen uptake, processing, and presentation abilities. Fully mature DCs can process tumor-associated antigens into small peptide fragments, bind them to major histocompatibility complexes (MHC), and display them on their cell surface. This presentation activates naive T cells, releasing cytokines such as interferon - γ, initiating adaptive immune responses, and effectively clearing tumor cells[22].

Along with type I interferon, the cGAS-STING pathway can also activate NF-κB, which results in the production of a number of inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β). IL-6 controls T cell development and function in addition to boosting the anti-tumor activity of CTL and NK cells. By encouraging immune cell recruitment and activation, IL-1β can kill tumor cells. By activating endothelial cells, TNF-α can alter the permeability of the tumor vasculature and directly cause tumor cells to undergo apoptosis. This change increases the immune cells' anti-tumor effects by facilitating their penetration into the tumor tissue[23].

3.3. Immunotherapy

Activating the STING pathway can greatly boost anti-tumor immune responses already present in tumors with high immunogenicity, increase the quantity and activity of T cells specific to the tumor, improve the efficacy of immunotherapy to kill tumor cells, and more[24].

However, in the case of cancers with low immunogenicity, the presence of several immunosuppressive agents in the tumor microenvironment and the limited expression of surface

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antigens on tumor cells lead to poor immunotherapy efficacy[25]. In this instance, tumor cells may experience immunogenic cell death as a result of STING pathway activation. Tumor cells will emit certain damage-related molecular patterns during this process, which will also stimulate the immune system, draw immune cells to the tumor site, and increase the tumor cells' antigenicity, which will make T cells more likely to detect them. Furthermore, by controlling the makeup and activity of immune cells inside the tumor microenvironment, the STING pathway can create an environment that supports immune cell function and overcomes the immunogenic tumors' resistance to immunotherapy[26].

The activation of the STING pathway presents a novel target for combination therapies in tumor immunotherapy. By integrating with diverse treatment modalities, including radiotherapy, chemotherapy, oncolytic virus therapy, etc. to produce synergistic anti-tumor effects. This combination therapy can not only improve the control rate of local tumors, but may also have an immune killing effect on distant metastatic tumor cells, providing a broader idea and strategy for the comprehensive treatment of tumors.

4. Summary

The body's self-defense depends on the cGAS-STING signaling pathway being moderately activated, while overactivation can lead to inflammatory illnesses and autoimmune reactions. The severe autoimmune condition known as Aicardi-Goutières syndrome is brought on by the STING signaling pathway's ongoing aberrant activation. A significant amount of double-stranded DNA (dsDNA) is released by apoptosis and cell destruction in patients with systemic lupus erythematosus. Type I interferons and other inflammatory factors are produced more frequently when cGAS recognizes these dsDNAs and activates STING and its downstream signaling pathways. Rheumatoid arthritis patients' cells may exhibit an aberrant buildup of nucleic acids in an inflammatory milieu, which can trigger the cGAS-STING pathway and raise the synthesis of inflammatory factors[27].

Currently, several small molecule agonists targeting the cGAS-STING pathway are under development. These agonists can directly activate the STING protein, mimicking the function of cGAMP. In preclinical studies, these agonists have shown significant anti-tumor effects in various tumor models, capable of inhibiting tumor growth and even causing complete regression in some tumors. Moreover, the combined application of cGAS-STING pathway activators with other tumor treatment methods has also made certain progress[28]. The anti-tumor immune response can be strengthened and the drawbacks of monotherapy can be overcome with this combined treatment approach. It is anticipated that cGAS-STING pathway activation will develop into a novel tumor immunotherapy tactic. Activating the cGAS-STING pathway may boost the body's anti-tumor immune response in tumor patients who don't react well to conventional immunotherapy. The activation of the cGAS-STING pathway can use the substantial amount of dsDNA released by tumor cells themselves to initiate an immune response, boosting the body's immune surveillance and tumor-killing capabilities, particularly in tumors with high mutational burdens like lung cancer and melanoma. The application potential of cGAS-STING pathway activation in additional tumor types and the potential for combination use with other cutting-edge therapeutic technologies will be further investigated in future studies[29], providing more treatment options for tumor patients and expanding the new field of tumor immunotherapy.

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