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Exploration of Tumor Immunotherapy Strategy Based on STING Signaling Pathway

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ABSTRACT

With the rapid development of tumor immunotherapy, the quality of life of tumor patients has been greatly improved, but the low response rate and drug resistance of individual treatment methods still plague clinical practice. The interferon gene stimulating factor signaling pathway discovered in recent years serves as an important bridge between innate immunity and adaptive anti-tumor immunity, and is currently a highly promising new target for tumor immunotherapy. This pathway can be activated by abnormal DNA in the cytoplasm, inducing strong expression of type I IFN and pro-inflammatory cytokines, and reshaping the immunosuppressive tumor microenvironment, thereby transforming cold tumors into hot tumors in immunology. This article aims to systematically elucidate the combination therapy approach guided by the STING pathway, summarize the types and development of STING agonists, and provide a detailed summary of the methodological basis, synergistic mechanisms, and latest research progress of the combination use of STING agonists with other immune checkpoint blockers, radiotherapy and chemotherapy drugs, tumor vaccines, targeted therapy drugs, and other congenital immune agonists, cell therapy, etc. Finally, summarize the current status and future research directions of the research field in which this article is located. By rational design and optimization of joint strategies, targeting the STING pathway is expected to overcome the limitations of existing immunotherapy and bring clinical benefits to more cancer patients.

KEYWORDS

STING signaling pathway; Tumor immunotherapy; Combination therapy; Immune checkpoint inhibitors; Tumor microenvironment; cGAS

1. INTRODUCTION

In the past decade, tumor immunotherapy, including immune checkpoint inhibitors and chimeric antigen receptor T cell therapy, has achieved unprecedented success in the treatment of many malignant tumors and can provide long-term benefits to some patients; However, low objective response rates and primary and/or acquired drug resistance are still common phenomena. Therefore, the search for new immunotherapy targets and the adoption of new combination therapies to benefit more patients have become the unremitting goals of researchers [1]. The interferon gene stimulator pathway is a newly discovered pathway in recent years and has played an important role in this study.

STING is one of the important pathways of innate immune response. As an intracellular DNA receptor, it induces a large amount of type I IFN response after discovering genomic instability, pathogen invasion, and cytoplasmic DNA caused by certain treatment methods, and participates in the first line of defense and anti-tumor immune monitoring and effects in the antiviral response process. It can effectively activate antigen-presenting cells and induce tumor specific T cell initiation and infiltration, as well as reverse the immunosuppressive state in the tumor microenvironment.

Therefore, targeted activation of the STING pathway is considered a powerful means of igniting anti-tumor immune responses and overcoming immune tolerance [2].

2. OVERVIEW OF STING SIGNALING PATHWAY

STING is a highly evolutionarily conserved natural immune signaling pathway that primarily detects unwanted DNA in the cytoplasm and initiates a series of defense responses guided by type I IFN. The activation of STING begins with the detection and binding of cytoplasmic DNA by CGAS. When DNA invasion is induced by tumor cells or other cells (including pathogens) or therapy, cGAS catalyzes ATP and GTP to form a second messenger cyclic dinucleotide. CGAMP is an important signaling molecule that binds to the transmembrane protein STING on the endoplasmic reticulum, causing conformational changes and the formation of oligomers.

The activated STING protein is shed from the ER and transferred to the perinuclear compartment via Golgi apparatus, where it recruits and activates downstream serine threonine kinase TBK1 (TANK Binding Kinase 1). TBK1 then phosphorylates IRF3 to form a dimer and enters the nucleus. Phosphorylated IRF3 in the nucleus works in synergy with transcription co activators to initiate efficient expression of type I interferon genes. In addition, STING signaling can activate the nuclear factor kappa B pathway and promote the production of many inflammatory cytokines [3].

In the context of tumor immunity, this pathway undergoes a series of cascade reactions after activation, playing important roles in multiple aspects of anti-tumor immune response: type I interferon released by tumor cells or tumor related immune cells is an effective immune adjuvant; It can effectively promote DC maturation and its antigen presentation function, especially helping to deliver tumor associated antigens to initial CD8+T cells, which is also the first step in activating adaptive anti-tumor immunity.

Secondly, type I IFN and chemokines can directly affect the TME's ability to attract immune cells (including cytotoxic T lymphocytes and NK cells) to infiltrate tumors and enhance their killing activity. In addition, the activation of STING can also induce ICD in some tumor cells, producing more antigens and DAMPs after tumor cell apoptosis or necrosis. Thereby enhancing immune signaling.

Finally, sustained IFN signaling is beneficial for resisting various immunosuppressive factors in the tumor microenvironment, including Treg and MDSCs, and can transform immunosuppressive cold tumors into immune activated hot tumors, providing a good prerequisite for future immunotherapy [4].

3. DEVELOPMENT AND CLASSIFICATION OF STING AGONISTS

Based on the recognition of the anticancer effect of the STING pathway and the need for further exploration, people have begun to seek effective artificial agonists that can activate the STING pathway as a clinical translation direction. Based on the structural characteristics of compounds, STING agonists can be roughly classified into the following types, and new delivery methods for agonists have also been derived during the development process [5].

The first category is CDN and its derivatives, which simulate the structure of the natural second messenger cGAMP. ADU-S100 is an early representative substance that has been explored in clinical practice for the treatment of cancer through intratumoral injection, and has shown good efficacy in preclinical models. But the problem with natural CDN molecules is that they are difficult to penetrate the cell membrane; Easy to be hydrolyzed and destroyed by phosphodiesterase; Intravenous administration can cause significant toxic reactions. In order to overcome the above bottlenecks, researchers have chemically modified molecules to obtain dinucleotide derivatives containing non classical phosphodiester bonds, thereby improving the stability and activity of such drugs in vivo.

The second type is small molecule STING agonists without CDN structure, which can be obtained through HTS or structure based design. They are structurally completely different from natural CDNs and can directly interact with STING proteins to activate STING. DMXAA was once considered a vascular disruptor and was later proven to be an effective mSTING agonist in later studies. Unfortunately, it is ineffective in human STING, and this species specificity limits its development for clinical applications. And new small molecule agonists such as MSA-2 have the characteristics of effectively activating human STING and good oral bioavailability, which can achieve systematic administration [6].

However, even with the continuous improvement of agonists themselves, how to effectively and safely deliver them to target cells remains a huge challenge. Although intratumoral injection has high local concentration and low systemic toxicity, it is limited to superficial or palpable tumors and is invasive. To solve this problem and apply it to more areas, including metastatic lesions, a new delivery system has been developed. The most promising method among them is to use nanoparticle delivery systems. Encapsulating STING agonists in liposomes, polymer nanoparticles, or inorganic nanocarriers can not only protect them from degradation and prolong their half-life, but also passively enrich them in tumors through EPR effect, or actively enrich them in tumors through surface modification.

4. STRATEGIES AND MECHANISMS OF STING PATHWAY COMBINATION THERAPY

4.1. Combined Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (such as antibodies targeting PD-1 and its ligands, as well as CTLA-4) restore T cell anti-cancer activity by eliminating inhibitory signals. However, the effectiveness of such drugs largely depends on the pre-existing effector T cells that have infiltrated into the tumor. The combination of STING agonists and immune checkpoint inhibitors is considered a complementary strategy [7].

The most crucial aspect is that STING agonists can act as immune promoters, transforming immunosuppressive cold tumors into T cell enriched hot tumors, providing the necessary immune cell foundation and inflammatory microenvironment for immune checkpoint inhibitors to exert their effects. Intratumoral injection of STING agonists induces local production of large amounts of type I interferon, promotes DC maturation, and presents tumor antigens to T cells in the draining LN, activating and amplifying tumor specific T cell clones; Newly generated effector T cells infiltrate the tumor under the influence of chemokines.

However, in the tumor microenvironment, immune checkpoint molecules are often highly expressed, leading to premature depletion of infiltrating T cells. The combined application of ICIs can block negative pathways such as PD-1, protecting newly generated T cells from the inhibitory effects of the tumor microenvironment and rendering them ineffective, thereby effectively connecting immune activation with the immune sustained phase. Most studies in vitro and animal models have shown that this treatment regimen can significantly inhibit tumor progression and generate significant immune memory responses to prevent recurrence in various tumor mouse models.

4.2. Combination Radiotherapy and Certain Chemotherapy Drugs

Radiation therapy and certain types of chemotherapy drugs are not only direct means of killing tumor cells, but can also exert distant effects by inducing immunogenic cell death. The generation of this effect is closely related to the activation of the STING pathway. Radiation or specific chemotherapy drugs such as anthracyclines and platinum based drugs can cause extensive DNA damage in tumor cells, leading to chromosomal instability or cell death, thereby releasing a large amount of DNA

fragments into the cytoplasm or tumor microenvironment. These endogenous injury related molecular patterns can be recognized by cGAS in antigen-presenting cells, especially dendritic cells, which subsequently activate the STING signaling pathway and trigger type I interferon response. Therefore, radiotherapy and chemotherapy provide abundant upstream signal sources for the activation of STING [8]. In this joint strategy, radiotherapy or chemotherapy plays the role of immune trigger, while exogenous STING agonists act as signal amplifiers. It can further enhance and expand the innate immune response induced by treatment, promote stronger antigen cross presentation and T cell activation. Research has shown that compared to monotherapy, combination therapy not only effectively controls tumors in locally irradiated or treated areas, but also inhibits distant metastases that have not been directly treated through systemic immune activation, resulting in significant distant effects. This strategy combines the local cytotoxic effects of traditional therapies with STING mediated systemic immune activation, providing a new approach for the treatment of metastatic cancer.

4.3. Combined Tumor Vaccine

The goal of tumor vaccines is to induce a long-lasting protective immune response in the body by providing tumor specific antigens. But the effectiveness of vaccines relies heavily on effective immune adjuvants to stimulate the innate immune system and promote APC maturation. STING agonists themselves are highly efficient intrinsic immune activators, making them potential adjuvant candidates for tumor vaccines. Simultaneous delivery of tumor antigens by STING agonists can establish a highly inflammatory environment at the injection site, where the production of local type I IFN strongly drives the activation of DCs and their migration towards DLNs [9].

This activated DC can better uptake and process vaccine antigens and effectively present antigen peptides to initial T cells, causing strong and specific CD8+and CD4+T cell responses. This combined effect can compensate for the shortcomings of traditional aluminum adjuvants that mainly stimulate humoral immunity, and is very beneficial for stimulating strong cellular immunity, which is an important pathway for clearing tumor cells.

Whether it is peptide vaccines based on new antigens, vaccines based on viral vectors, or cell vaccines based on dendritic cells, the combination with STING agonists has shown enhanced tumor prevention and treatment effects in preclinical models, and helps establish long-lasting immune memory.

4.4. Combined Targeted Therapy

With the deepening understanding of tumor molecular biology, more and more targeted drugs targeting specific oncogenic signaling pathways have been developed, and some targeted drugs have unexpectedly synergistic effects when combined with STING agonists. The most typical representative among them is poly (ADP ribose) polymerase inhibitor. PARP inhibitors have a synthetic lethal effect in tumors with homologous recombination repair defects, but their efficacy may be limited. The activated cGAS STING pathway in PARP inhibitor induced DNA damage can be amplified by STING agonists.

On the one hand, the combination increases the direct killing effect on tumor cells, and on the other hand, due to the enhancement of IFN response and T cell activation, simple cytotoxic therapy has become an immunomodulatory treatment. Another approach is to use anti vascular drugs in combination. Abnormal tumor blood vessels hinder immune cell infiltration. Antivascular drugs can normalize chaotic tumor blood vessels, optimize blood flow and oxygenation at the tumor site, and thus facilitate STING agonist stimulated effector T cells to reach the tumor interior and exert their effects.

In addition, its combination with epigenetic drugs such as DNA methyltransferase inhibitors or histone deacetylase inhibitors has also attracted attention. These drugs can upregulate the expression

of endogenous retroviral elements, leading to the accumulation of double stranded RNA and DNA in the cytoplasm, spontaneously activating the cGAS STING pathway, and synergizing with exogenous agonists.

4.5. Combination with Other Innate Immune Pathway Agonists

The innate immune system contains multiple pattern recognition receptor families that can recognize various pathogen related molecular patterns or injury related molecular patterns. In addition to cGAS STING, the Toll like receptor family and the retinoic acid-induced gene I like receptor family are also important immune activation pathways. In theory, simultaneous activation of multiple innate immune pathways may result in overlapping or even synergistic effects, awakening the immune system more comprehensively. For example, TLR3 agonist poly (cytidine) can mimic viral double stranded RNA to activate the TLR3-MAVS pathway, while RIG-I agonist can directly activate the RIG-I-MAVS pathway, both of which can induce the production of type I interferon and pro-inflammatory cytokines. Combined with STING agonists, activation signals can be simultaneously inputted from both DNA and RNA sensing pathways, which may induce a broader and stronger cytokine spectrum and activate a more diverse subset of immune cells, thereby more effectively breaking the immune tolerance state of tumors [10].

However, this combination may also significantly increase the risk of immune related toxicity such as cytokine storms, thus requiring precise dose and timing exploration.

4.6. Combined Cell Therapy

Adoptive cell therapy, represented by chimeric antigen receptor T cell therapy, has achieved great success in hematological tumors, but faces challenges in solid tumors such as immune suppression in the tumor microenvironment and insufficient T cell persistence. The combination of STING agonists and cell therapy aims to create a more favorable combat environment for the reinfused immune cells. On the one hand, systemic or local administration of STING agonists can reshape the tumor immune microenvironment by inducing type I interferon to suppress immunosuppressive cells, increasing chemokine expression to promote CAR-T cell infiltration, and enhancing antigen presentation, thereby improving CAR-T cell homing and function in solid tumors. Another more advanced approach is to genetically engineer the cell therapy itself, such as constructing CAR-T cells that express constitutive activating STING proteins or can produce cGAMP.

These modifications enable CAR-T cells to not only directly exert killing effects after recognizing tumor antigens, but also activate the STING pathway through local autocrine or paracrine pathways, thereby self creating and maintaining a pro-inflammatory microenvironment that supports their survival, expansion, and function, achieving a self enhancing anti-tumor cycle, which is expected to significantly improve the efficacy of solid tumors.

5. CONCLUSION

Therefore, the STING signaling pathway is an important bridge connecting genomic instability and anti-tumor adaptive immunity in tumor cells, and has become one of the most promising targets for novel tumor immunotherapy; However, given the diversity and complexity of tumor immune escape pathways, it is difficult to achieve broad and lasting therapeutic effects solely targeting the STING signaling pathway. Therefore, using STING as a target for combination therapy has become a new research direction and shows great prospects.

This article summarizes the synergistic effects and research status of STING agonists combined with immune checkpoint inhibitors, radiotherapy and chemotherapy, tumor vaccines, targeted drugs, other innate immune agonists, and cell therapy. The basic principle of the above strategies is to use STING

agonists as switches to trigger and amplify immune responses, providing a favorable immune environment for other therapies or directly enhancing their effects, playing a complementary and synergistic role at different levels, achieving a more comprehensive and in-depth attack on tumors.

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