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Research Progress in the Mechanism of Functional Regulation of STING

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Abstract: *Interferon type I (IFN-I) plays a key role in intrinsic immunity against viruses and its production is associated with the recognition of intracytoplasmic non-self DNA by the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon gene (STING) signalling pathway, as well as the recognition of downstream kinases TBK1 and interferon regulatory factor 3 (IRF3), which are the core of this signalling pathway. As the core part of this signalling pathway, its modification and stability are crucial for the correct and effective generation of immune response. There are three main regulatory mechanisms of STING: one is to promote or inhibit the STING signalling pathway through ubiquitination modification, the other is to regulate the duration and intensity of STING activation through phosphorylation. The third is to regulate the stability of the STING-TBK1 complex. The understanding of the regulatory mechanisms of STING function provides new avenues for the treatment of viral and inflammatory diseases.*

Keywords: *Stimulator of Interferon Genes, Innate Immunity, Signalling Pathway, Interferon Type I*

1. Introduction

Innate immunity is the body's first line of defence against invading pathogens, capable of rapidly recognizing pathogens and producing type I interferon I (IFN-I) and other cytokines to suppress infection. The stimulator of interferon gene (STING) is a membrane receptor protein that connects cytoplasmic microbial nucleic acids to downstream cytokines produced when pathogen DNA, organismal aberrant DNA, or cyclicdinucleotide (CDN) is inhibited by intracytoplasmic DNA receptors such as cyclic GMP-AMP synthase (cGMP-AMP synthase, cGMP-AMP synthase, cGMP-AMP synthase, cGMP-AMP synthase, cGMP-AMP synthase, and other cytokines. When STING is recognized by intracytoplasmic DNA receptors such as cyclic GMP-AMP synthase (cGAS), the STING signalling pathway is activated to promote the expression of IFN. Abnormal expression of STING may cause immunodeficiencies or autoimmune diseases, and therefore STING is subjected to sophisticated regulation by various regulatory mechanisms, and plays a key role in the antiviral immunity of the organism.

2. Mechanisms of STING Function Regulation

2.1 Ubiquitination Modification of STING

Ubiquitin is a versatile molecular marker that regulates different cellular processes through proteasome-dependent and non-dependent mechanisms. Ubiquitin itself contains seven lysine sites: K6, K11, K27, K29, K33, K48, and K63, each of which can bind to another ubiquitin, and the different linkages of the polyubiquitin chain determine the specific physiological or pathological function of the target protein [1]. Current studies on the ubiquitination modification of STING mostly focus on K48-mediated protein hydrolysis and K63-mediated regulation.

2.1.1 K48-mediated Ubiquitination of STING

The E3 ubiquitination ligases identified to date that ubiquitinate STING through K48-mediated modification include ring finger 5 (RNF5), tripartite motif protein (TRIM) 30a, and TRIM29, all of which

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depend on this function.

Ubiquitination of STING by RNF5 and TRIM30a to inhibit sustained innate immune responses RNF5 is a key component of the endoplasmic reticulum-associated degradation (ERAD) ubc6/p97 network [2], which is involved in cellular activity, control of endoplasmic reticulum protein amount, cancer, degenerative myopathy and other physiopathological processes. After organisms are infected with Sendai virus, the E3 ubiquitination ligase RNF5 interacts with STING and ubiquitinates it at the lysine 150 site of STING, a process that leads to proteasome-dependent degradation of STING, which inhibits interferon rregulatory factor 3 (IRF3) activation and IFN-β production to avoid a sustained uncontrolled innate immune response [3]. However, the ubiquitination of STING by RNF5 can be inhibited by another member of the same family, ring finger 26 (RNF26), which ubiquitinates STING at the same site as RNF5 through K11 mediation, resulting in attenuation of the modification of STING by RNF5 and its subsequent proteasome-dependent degradation [4].

Another ubiquitination modification of STING to inhibit the sustained intrinsic immune response is TRIM30a, an E3 ubiquitination ligase of the TRIM family, which can inhibit antiviral innate immune responses activated by the STING signalling pathway by using its cyclic structure [5].The pathway of degradation of STING by TRIM30a is similar to that of RNF5, and it is similarly reversed by the proteasome inhibitor MG132. This result was also validated in TRIM30a-deficient mice and L929KO cell line. Moreover, by injecting herpes simplex virus 1 (HSV-1) into TRIM30a-deficient mice, we found that the inhibitory effect of TRIM30a on STING was not only limited to dendritic cells, but also increased the expression of IFN and IL-6 expression was increased in the brain, lung, liver and abdominal macrophages of the defective mice, and the replication of HSV-1 genomic DNA was significantly inhibited. Thus, the inhibition of the STING signalling pathway by TRIM30a is systemic and multi-organic.

Ubiquitination modification of STING by TRIM29 to maintain sustained viral infection. TRIM29, another molecule of the TRIM family, after induced upregulation of its expression during EBV infection, ubiquitinates STING at its lysine 370 site and promotes its proteasome-dependent degradation, which inhibits the downstream production of IFNs and the killing of nasopharyngeal carcinoma cells, leading to EB virus immune escape and nasopharyngeal cancer development and progression [6].

2.1.2 K63-mediated Ubiquitination Modification of STING Promotes Anti-disease Innate Immune Response to Viruses

Unlike the K48-mediated ubiquitination process, K63-mediated polyubiquitination mainly regulates non-protein hydrolysis processes such as membrane translocation and signal transduction. The molecules known to ubiquitinate STING via K63 are TRIM32 and TRIM56.

Ubiquitination of STING by TRIM32 promotes the interaction of STING with TBK1. TRIM32, another member of the TRIM family, promotes the interaction of STING with TBK1 by using its N-terminal ring domain to exert its E3 ubiquitinating enzyme activity at the lysine 20/150/224/236 sites of STING via the K63-mediated pathway and thus increased IFN expression, positively regulating the body's intrinsic immune response against DNA and RNA viruses [7].

Ubiquitination modification of STING by TRIM56 promotes dimer or oligomer formation of STING to recruit TBK1. TRIM56 is an interferon-inducible gene that is up-regulated by double-stranded DNA stimulation, and ubiquitinates STING via the K63 polyubiquitin chain at the lysine 150 site, a process that promotes the formation of dimers or oligomers of STING for recruitment of TBK1, which in turn promotes the production of IFN [8]. It has been found that TRIM56 promotes an inherent antiviral immune response by ubiquitination modification of cGAS at the lysine 335 site, leading to the formation of dimers with a significant increase in its ability to bind DNA and promote cGAMP formation. Although the N-terminal regulatory region of cGAS was thought to have no specific physiological function, recent studies have revealed that the N-terminal RD region can expand the range of DNA recognition by full-length cGAS, increase the binding efficiency of dsDNA, as well as efficiently activate the STING/IRF3-mediated signalling pathway for recognition of DNA in the cytoplasm [9]. Therefore, the interaction between TRIM56 and cGAS may depend on its C-terminal atypical NHL structure and N-terminal RD region, respectively [10].

2.1.3 K27-mediated Ubiquitination Modification of STING

An increasing number of studies have demonstrated the K27-mediated ubiquitination modifications of STING. Autocrine motilityfactor receptor (AMFR) and insulininduced gene 1 (INSIG1), which both contribute to the K27-mediated ubiquitination of STING. AMFR is a ubiquitinating enzyme localized in

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the endoplasmic reticulum membrane that promotes polyubiquitination of ERAD-targeted proteins [11]. In the endoplasmic reticulum of all eukaryotic organisms, a specialized quality control system exists to maintain protein homeostasis and prevent the accumulation of aberrant proteins and the secretion of harmful substances [12]. Endoplasmic reticulum protein amount control is achieved by degradation of endoplasmic reticulum-associated proteins. When exogenous DNA in the cytoplasm is recognized, AMFR and INSIG1 on the endoplasmic reticulum membrane form an E3 ubiquitin chain complex that is recruited by STING, which promotes K27-mediated ubiquitination of STING, and at the same time, this process also provides an anchoring platform for TBK1 to bind with STING [13], which promotes the formation of STING-TBK1 complexes and the activation of downstream signalling pathways.

2.2 Phosphorylation Modification of STING

Unlike the ubiquitination modification of STING, the phosphorylation modification of STING has not been studied in sufficient depth, and it has now been found that the activation of serine/threonine kinase (LKB1)-adenosine 5' -monophosphate-activated protein kinase (AMPK)-Unc-51 like utophagy activating kinase 1 (ULK1) signalling pathway phosphorylates STING and promotes its degradation to avoid sustained immune responses and spontaneous immune disorders. STING activation is associated with cyclic CDN produced by specific intracellular bacteria as well as the DNA-binding protein cGAS, in addition to DNA in the cytoplasm [14]. CDN, while promoting STING activation, can form a negative feedback mechanism to prevent sustained intrinsic immune responses and inflammatory diseases [15]. When the organism is unstimulated, upstream LKB1 maintains the phosphorylation of threonine 172 of the AMPK-activated catalytic subunit α1, and phosphorylated AMPK phosphorylates serine 556 of ULK1 to inhibit its function. Upon bacterial or viral invasion, cGAS activates ULK1 by dephosphorylating AMPK using the non-classical cyclic 2‘-5’ cGAMP generated by GTP and ATP [16]. cGAS activates ULK1 in the STING-TBK1 complex during transport from the endoplasmic reticulum. During translocation of the STING-TBK1 complex from the endoplasmic reticulum to the Golgi, ULK1 phosphorylates and modifies STING at serine 366, a process that results in lysosomal degradation of STING after TBK1 is translocated to the nuclear endosome and lysosome, which inhibits the sustained intrinsic immune response. Recently, RIG-I and IL-6 have also been found to negatively regulate the STING signalling pathway by phosphorylating STING through an ULK1-dependent pathway [17].

2.3 Regulating the Stability of the STING-TBK1 Complex

Upon recruitment of activated STING to TBK1, TBK1 phosphorylates and modifies STING at several serine and threonine sites, including serine 366 [18], and phosphorylated STING is essential for subsequent phosphorylation of IRF3 by TBK1. Thus, the stability of the STING-TBK1 complex influences the activation of downstream signalling pathways and the generation of an effective immune response.

2.3.1 Inhibition of STING-TBK1 Complex Stability by NLR

It has been reported that the nucleotidebinding domain (NBD) of NLRC3 directly binds to the membrane localisation-related region of STING, which attenuates the interaction of STING with TBK1. At the same time, the migration of STING to the nucleus and punctate regions is blocked, inhibiting the activation of downstream signalling pathways. Another member of the NLR family, NLRX1, through its NBD, can also bind to the membrane localization-related region of STING, which is a key component of the NLR family. NLRX1, another member of the NLR family, also binds to STING through its NBD to block the formation of the STING-TBK1 complex, thereby inhibiting TBK1 activation and IFN production [19].

2.3.2 Promotion of STING-TBK1 Complex Stability by ZDHHC1, iRhom2

In contrast, zinc finger aspartate-histidine-histidine-cysteine domain containing 1 (ZDHHC1), which contains the DHHC region, was able to enhance the recruitment of STING to TBK1 and IRF3 by enhancing the dimerisation of STING and promoting IFN-β production [20]. Other molecules that enhance the interaction between STING and TBK1 are inactive rhomboid protein 2 (iRhom2). iRhom2 recruits signal sequence receptor subunit 2 (SSR2), also known as TRAPβ, to STING [20] to activate STING and promote its translocation. iRhom2 also recruits the deubiquitinating enzyme EIF3S5 to remove the K48 ubiquitination chain-mediated ubiquitination of STING to maintain the stability of STING-TBK1, ultimately resulting in the positive regulation of the STING-mediated intrinsic antiviral immune response. iRhom2 also recruits EIF3S5 to remove K48 ubiquitination chains from STING to maintain STING-TBK1 stability.

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3. Roles of STING Function Regulation in Understanding of Disease Mechanisms and Diagnosis and Treatment of Diseases

Studies on the mechanisms regulating STING function have provided new therapeutic avenues for antiviral and anti-inflammatory treatments. Currently, the most prominent approach is to activate the STING signalling pathway by introducing CDN to counteract the process of infection or tumor progression. At the same time, inhibiting STING activation for underlying autoimmune diseases can lead to symptomatic improvement [21].

3.1 Virus Immune Escape by Inhibiting STING

Given the critical role of STING in the host's antiviral immune response, many viruses have evolved defences that inhibit IFN-I production and evade host cell attack by targeting STING. HBV, human T-lymphoblastic leukaemia virus type I and Yersinia pestis outer proteins all block K63-mediated ubiquitination of STING modification to evade intrinsic immune attack and establish persistent infection in host cells [22-24]. The HCV membrane protein NS4B can inhibit STING-mediated signalling by interfering with the interaction between STING and TBK1 [25]. The study of how viruses target STING to evade the host cell defense system will help to increase the understanding of the molecular mechanisms of host antiviral immune responses and provide new therapeutic targets for the treatment of virus-associated diseases.

3.2 STING and Related Molecules can be used as Target Molecules for the Treatment of Tumors or Autoimmune Diseases

It has been successively reported in the literature that the expression level of STING is reduced in colon cancer cell lines and melanoma cell lines [26-27] and the same phenomenon has also been verified in hepatocellular carcinoma and gastric cancer [28-29]. In the process of tumor development, IFN is dependent on the cGAS-STING pathway to activate CD^{8+} T cells. Direct stimulation of either tumor-generated DNA or STING ligands can promote IFN-I production by dendritic cells, suggesting that STING-induced therapies may be potential anti-tumor tools [30-31]. However, STING does not exert an inhibitory effect on all tumors, but STING expression is up-regulated in human papillomavirus-associated tumors [28], so the effect of STING on tumorigenesis and progression may be tumor-specific. Since the STING signalling pathway is essential in the activation of tumor-specific CD^{8+} T cells and the elimination of tumors, activation or inhibition of the STING signalling pathway in conjunction with the use of anti-tumor vaccines or conventional radiotherapy may provide new avenues and specific therapeutic targets for the treatment of different types of tumors.

Persistent or excessive presence of cytoplasmic DNA causing sustained production of IFN-I is one of the major causes of chronic inflammation and autoimmune diseases. Overactive IFN-I-type responses activate cytotoxic immune cells through IFN-inducible genes, which in turn promote the sustained release of pro-inflammatory cytokines such as IL-1α/β, IL-12, and TNF-α, resulting in excessive inflammation and tissue damage [32]. It has been found that DNA produced by keratinocyte damage induced by UV irradiation can inhibit the phosphorylation of STING by ULK1 and cause a sustained immune response, which may be the cause of UV-induced and exacerbated SLE [33]. In another spontaneous immune disease with basal nucleus calcification encephalopathy (Aicardi-Goutièressyndrome (AGS)), the sustained expression of IFN-I has also been found to be possibly dependent on the cGAS-STING signalling pathway [34]. The main approaches to ameliorate STING-induced autoimmune disease are JAK inhibitors and inhibition of B-cell responses [35-36]. The JAK inhibitor tositinib inhibits STAT 1/2 dimer activation and thus IFN-stimulated gene transcription, whereas inhibition of B-cell responses prevents the overexpression of autoantigens. However, the efficacy of JAK inhibitors remains controversial because they suppress the protective STING-dependent intrinsic immune response. New therapeutic pathways and therapeutic targets remain to be further discovered and investigated.

4. Conclusions

Research on the mechanisms regulating STING function has led to a deeper understanding of STING. STING, a core member of the IFN-I pathway, is highly regulated in order to generate an effective immune response and clear pathogenic microorganisms from the body, while avoiding autoimmune diseases caused by over-immunity. Ubiquitination and phosphorylation modifications of STING, as well as

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STING-TBK1 complex stabilisation, have been shown to be the key mechanisms of STING's function in the IFN-I pathway. The ubiquitination and phosphorylation modifications of STING and the stability of the STING-TBK1 complex play a key role in the ability of the organism to generate a correct immune response. In the future, studies should focus on the following two aspects of STING function regulation: firstly, in-depth and comprehensive understanding of the regulatory mechanism of STING function, not only to discover new regulatory molecules and mechanisms, but also to conduct in-depth research on the mechanisms that have already been discovered. For example, it has been found that after HCMV infection, IE86, an early rapid response protein encoded by UL122, inhibits the 2D proteasome-dependent degradation of 2D proteasomes by increasing STING proteasome-dependent degradation and inhibits 2'-3'cGAMP-mediated production of IFN-β and CXCL10, thereby causing immune escape [37]. Whether IE86 binds directly to STING or utilizes other E3 ubiquitin ligases in this process needs further study and evidence. In addition, besides K48 and K63-mediated ubiquitination modifications, are there other molecules involved in other pathway-mediated ubiquitination modifications? Is there any interaction between ubiquitination modifications and phosphorylation modifications of STING? What is the role of STING function in pathogenic infections and immune diseases? All these questions need to be studied in depth. The second is to propose new ideas for diagnosis and treatment of related diseases based on the discovered molecules and mechanisms. These two aspects of research will help to more comprehensively understand the role of STING in the intrinsic immune response and its molecular mechanisms, and provide a theoretical basis for understanding host-pathogen interactions, exploring the pathogenesis of autoimmune diseases, and searching for new therapeutic targets.

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