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A New Aspect of STING that Promotes IgE Production in Allergic Asthma

Yusuke Murakami and Naomi Yamashita*

Department of Pharmaceutical Sciences and Research Institute of Pharmaceutical Sciences, Musashino University, Tokyo, Japan

Description

Stimulator of interferon genes (STING) is a DNA sensor, which recognizes cyclic-GMP and -AMP (cGAMP) synthesized by cyclic GMP-AMP synthase (cGAS) from pathogen's DNA and induces pro-inflammatory cytokines and type interferons [1-4]. Mainly, STING works as a "host-defender" against pathogen infection, but under some conditions, STING also recognizes self-DNA, such as genomic and mitochondrial DNA, and promotes inflammation. Even though STING plays a significant role in various inflammatory diseases, STING response to self-DNA is a topic of controversy in Systemic Lupus Erythematosus (SLE) model mice. One study has shown that STING signaling improves the inflammatory response in MRL-Faslpr mice [5]. Another study has reported that STING signaling activates conventional dendritic cells (cDCs) and induces differentiation of plasmacytoid DCs (pDCs), and thereby worsens the kidney inflammation in Fcgr2b-/-mice [6]. Therefore, the mechanism through which STING is involved in the inflammatory response to self-DNA is still unclear.

Allergic asthma is one of the most famous allergic diseases. There are 300 million asthmatics in the world, and the number of patients is increasing as a variety of allergens increases because of the global warming and changes in the living environment [7]. The onset of this disease is firstly caused by inhalation of various allergens including components from House Dust Mites (HDM), molds, and pets. Subsequently, antigen presentation of the allergens by dendritic cells differentiates naïve T cells to Type 2 helper T (Th2) cells and lymphocytes, eosinophils, basophils, and mast cells cooperatively induce allergic asthma [8]. Recently discovered type 2 Innate Lymphocytes (ILC2) also induces allergic inflammation without antigen presentation. Vigorous researchers have been conducted into the formation of allergic. Production of type 2 cytokines such as IL-13, IL-5, and IL-4 by Th2 cells and ILC2, as well as IgE production by activated plasma cells, are very important for the development of allergic asthma. In addition to these allergy relating factors, the latest research has focused on the involvement of innate immune receptors. Various cells expressing innate immune receptors (e.g., Toll-like receptors, TLRs) are involved in allergic asthma [9]. Recently, we analyzed STING protein levels in lung-infiltrating immune cells from HDM-sensitized mice and found that T and B lymphoid cells, dendritic cells, monocytes/macrophages, eosinophils, and neutrophils expressed STING. This result suggested that STING might be involved in the pathology of allergic asthma. However, there are few reports that STING is involved in the formation of pathology on allergic asthma. In 2019, Koji O et al. reported that synthesized cGAMP stimulation promoted HDM extract-induced allergic lung inflammation through IL-33 production [10]. This report suggests that the STING response promotes the pathology of asthma, but it is unclear how the endogenous STING ligand response is involved in the asthmatic pathology because only a synthesized-exogenous ligand is used in this report. To clarify the question, we evaluated how the response to STING endogenous ligands generated in allergic inflammatory conditions affected the pathology of asthma. Allergic asthma model was induced in C57BL/6 Wild Type (WT) and Sting-/- mice by intratracheally administrating HDM extract. As a result, there were no changes in total cell and eosinophil numbers of Bronchial Alveolar Lavage Fluid (BALF) in each mice group. But, interestingly, serum total and HDM-specific IgE titer in Sting-/- mice were significantly lower than those of WT mice [11]. Supporting these results, the percentages of total B cells in BALF and IgE+ B cells in Mediastinal Lymph Nodes (MLNs) were significantly lower in Sting-/- mice. But B cell proliferation by stimulating with HDM-extract was not altered between WT and Sting-/-mice. Previous studies have shown that STING enhances B cell receptor signaling and promotes antibody production [12,13]. When we stimulated WT mice with STING ligand, cGAMP, at the same time as HDM extract sensitization, the serum IgE titer and percentages of B cells in BALF significantly increased compared to HDM extract sensitization alone. These results suggest that STING signaling promotes the maturation of IgE-producing cells in allergic asthma.

How does STING signaling induce differentiation of immature B cells into IgE-producing cells in allergic asthma? We expected "Follicular helper T (Tfh) cells" as a candidate for the mechanism on STING-dependent B cell maturation because Tfh cells have several functions necessary to assist the maturation for B cells in the germinal center [14], and because these cells were less induced by transfer of autoreactive CD4+ T cells from Sting-/-mice [15]. Tfh cells express a chemokine receptor CXCR5 on the cell surface. CXCR5 response promotes migration of Tfh cells into lymphatic follicles and is important for interaction with B cells in the germinal center. Additionally, the immunosuppressive molecule PD-1 is also highly

***Address for Correspondence:** Dr. Naomi Yamashita, Department of Pharmaceutical Sciences and Research Institute of Pharmaceutical Sciences, Musashino University, Tokyo, Japan; Tel: +81-42-468-8647; Email: naoyama@musashino-u.ac.jp*

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expressed in Tfh cells. PD-1 also plays a role in regulating the activation of Tfh cells in the germinal center. This regulation is directly related to B cell selection.

Tfh cells produce IL-4, IL-21, and CXCL13, which are important for IgE production induced by T cell-dependent immune responses [16-18]. But in the murine model, IL-21 is known to strongly inhibit the differentiation and proliferation of Tfh cells. Therefore, IL-21 may function to promote IgE production only in humans. We analyzed the percentage of Tfh cells in MLNs by staining CD3, CD4, CD44, CD62L, PD-1, and CXCR5 in HDM-sensitized WT and Sting-/- mice. Percentage of Tfh cells in MLNs from HDM-sensitized Sting-/- mice was significantly lower than that of WT mice. Furthermore, the IL-4 expression level in Tfh cells was analyzed by cytokine staining. But IL-4 expression level was not altered between WT and Sting-/- mice. These results suggest that STING signaling promotes Tfh differentiation and/or proliferation in LNs, but not IL-4 production. In Figure 1, we show our proposed schema at present.

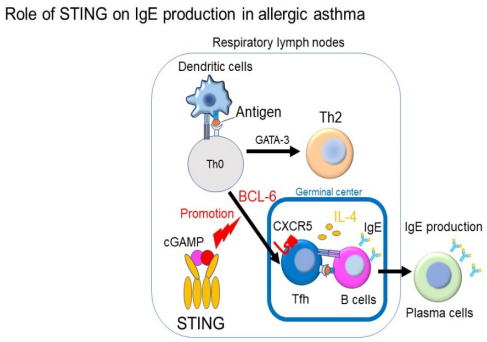

Figure 1. Role of STING on IgE production in allergic asthma.

The mechanism how STING signaling controls the number of Tfh cells needs to be resolved in the future. B-cell lymphoma 6 (Bcl-6) is an important transcription factor for differentiation naïve T cells into Tfh cells [18]. Tfh cells express high levels of the transcription factor Bcl-6 and a few cell surface molecules that are mainly required for the migration of Tfh cells to the germinal center. It would be very interesting if the STING expressed in T cells directly activates Bcl-6 and increases the number of Tfh cells.

Conclusion

In this review, we introduced a new aspect of STING: the importance of STING signaling for IgE production in allergic asthma. Our study suggests that STING is expressed on a variety of immune cells and that its role may vary depending on the pathology of diseases. If a new STING-regulating mechanism of IgE production is elucidated in the future, it may contribute not only to the progression of immunology but also to the development of therapeutic medicine.

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