

Letter to Editor

A hypothesis-effect of T cell epitope fusion peptide specific immunotherapy on signal transduction

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Received July 23, 2015; Accepted September 28, 2015; Epub October 15, 2015; Published October 30, 2015

Abstract: Asthma is a chronic nonspecific inflammatory disease of the airway primarily mediated by different inflammatory cells, including mast cells, eosinophils and T cells. We hereby specially focused on a signal pathway for Janus kinase-signal transducer and activators of transduction (JAK-STATs), which has been the interest of study in asthma since it more likely regulates cellular proliferation and differentiation, and consequently modulates immune system. In our consideration, knowledge on this signal pathway may provide an avenue for rational options in treatment of asthma on control of immune response basis.

Keywords: Allergic asthma, specific immunotherapy, signal pathway, JAK/STAT

Introduction

Asthma is a chronic nonspecific inflammatory disease of the airway primarily mediated by different inflammatory cells, including mast cells, eosinophils and T cells [1]. Currently, the signal pathway for Janus kinase-signal transducer and activators of transduction (JAK-STATs) has been the interest of study in asthma, because it governs cellular proliferation and differentiation as well as immuno-regulation [2].

Upstream stimulating factors for JAK/STAT6 pathway are involved in IL-4 and IL-13 that are crucial for pathogenesis of asthma. Previous studies demonstrated that, after activation of JAK/STAT6, IL-4 and IL-13, can lead to increased serum IgE levels and activation of lung fibroblasts, which are important properties of pathological changes in asthma attack [3, 4]. Combination of IL-13/IL-4 with IL-4RA is potentially enabling JAK1/JAK3 to phosphorylate, and in turn the phosphorylated JAK1/JAK3 further results in phosphorylation of Y575, Y603 and Y631 on the structure domain of IL4RA and STAT6. Under the interaction between the tyrosine phosphate and SH2 domain structure, the phosphorylated STAT6 tends to form dimers and translocates to the cell nucleus, where they regulate immune response after combination

with element of IL-4/IL-13 reaction gene promoter [5]. Additional animal experiments have proved that the function effect of Th2 cells rely on STAT6 signaling pathways. When STAT6 pathway in mice was activated, significantly boosted IL-4, IL-5 and IL-13 levels were seen in the alveolar lavage fluid of the mice, and the markedly increased levels demonstrated that Th2 response was dominant [6-8]. Some studies also revealed that the degree of Th2 cells activity is positively associated with the severity of a bronchial asthma.

STAT4 is a critical signal factor of Th1 cytokine, and totally disappeared immune response, eliminated INF- γ production capacity, weakened T cell proliferation and NK functions were observed in mice with STAT4 defects under IL-12 stimulus. Further observation suggests that the CD4⁺ T cells isolated from mice with defects of STAT4 can lead to cellular differentiation toward Th1 after CD4⁺ T cells being transfected onto the human STAT4 gene. This findings suggest that STAT4 is an important role in generation of Th1 cells [9, 10].

Specific immunotherapy (SIT) is currently recognized as the only approach to causal prophylaxis and treatment of asthma [11]. This principal involves regulation of antigen presenting

cells (APCs), T cell and B cell response, transformation of related subunit antibodies and inhibition of the effector cells (including eosinophils, basophils and mast cells) responsible for allergic inflammation. T cell epitope peptide, a peptide fragment extracted from natural allergens or recombinant T cell epitope, can make loss of T cell immunity or alterability of cytokine level, induce T cell immune tolerance, block B cell activation and IgE production [12].

On which basis, we have a hypothesis that tentative SIT may be achieved and verified in mouse models with allergic asthma via T cell epitope fusion peptide specific immune therapy on signal transduction.

SIT can not only effectively reduce the levels of allergen specific IgE antibody by blocking type I hypersensitivity reaction [13], but also reduce the CD4+ T cells to secrete IL-4, induce T cell differentiation from Th0 Th1 cells, and inhibit it to differentiate towards Th2 [14].

IL-4 only activates STAT6 in specific manner

Hideto Tozawa observed that IL-4 can significantly induce endothelial cell adhesion molecule 1 (VCAM 1). Since IL-4 regulation relies on production of VCAM 1 and secondary monocyte adhesion, which is primarily controlled by STAT6. These findings suggest that STAT6 plays pivotal part in regulating IL-4 signal transduction process [15]. In addition, IL-4 and IL-13 cytokines are in close link with the secretion of TH2 cells.

IL-12 specifically activates STAT4

In an experiment on the defects of IL-12R β 2 and STAT4 in mice by Kim et al., they found that airway hyperresponsiveness (AHR), response to non-eosinophilic inflammation and IFN- γ expression level were greatly disturbed. Contrarily, the effects were absent in mice with IL-4R α defects. These results showed that IL-13-mediated asthma phenotypes, such as AHR and non-eosinophilic inflammation, in the Th2 type asthma are dependent on the IL-12-STAT4-IFN- γ instead of IL-4R α -mediated signaling [16].

Conclusion and prospect

By the data described above, development of SIT vaccine for allergically asthmatic mice on T

cell epitope peptide basis shall be involved in determination of the signal pathways.

Nevertheless, we have to work out the pathway in connection of the upstream with the downstream in order to generate the signal transduction and therapeutic effects. This may rely on monitoring the changes of cytokines and signaling proteins before and after treatment in experimental animals, so that it is possible to analyze molecular mechanism of a fusion peptide in SIT, and provide the basis for treatment of allergic asthma induced by dust mite antigen with SIT. Thus, determination of the signal pathway shall be a novel and promising therapeutic approach to specific therapy of allergic asthma.

Acknowledgements

We wish to express our appreciation to Yu-Xin Jiang, Xiao-Dong Zhan, En-Tao Sun, Wei Guo, Ting Liu from the Department of Medical Parasitology, Wannan Medical University for their technical assistance in fulfillment of the experiment involved in this study and Mr. Xian-Yin Wang for language proofreading. This work was supported by the National Natural Science Foundation of China (No. 81270091), the Natural Science Foundation of Anhui Province (No. 070413088).

Disclosure of conflict of interest

None.

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