Immune Network
DOI 10.4110/in.2010.10.1.1
pISSN 1598-2629 eISSN 2092-6685
REVIEW ARTICLE

Role of IL-23 and Th17 Cells in Airway Inflammation in Asthma

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Asthma is characterized by chronic airway inflammation with intense eosinophil and lymphocyte infiltration, mucus hyperproduction, and airway hyperresponsiveness. Accumulating evidence indicates that antigen-specific Th2 cells and their cytokines such as IL-4, IL-5, and IL-13 orchestrate these pathognomonic features of asthma. In addition, we and others have recently shown that IL-17-producing $CD4^+$ T cells (Th17 cells) and IL-23, an IL-12-related cytokine that is essential for survival and functional maturation of Th17 cells, are involved in antigen-induced airway inflammation. In this review, our current understanding of the roles of IL-23 and Th17 cells in the pathogenesis of allergic airway inflammation will be summarized.

[Immune Network 2010;10(1):1-4]

INTRODUCTION

It is well established that there is a strong correlation between the presence of eosinophils and the presence of Th2 cells in the asthmatic airways and that classical Th2 cell-derived cytokines, namely IL-4, IL-5, and IL-13, play critical roles in orchestrating and amplifying allergic inflammation in asthma. In addition, several lines of evidence suggest that Th17 cells and their cytokines such as IL-17A and IL-17F are involved in neutrophil recruitment in severe asthma. Moreover, we have recently shown that IL-23-Th17 cell axis enhances Th2 cell-mediated eosinophilic airway inflammation. We will discuss the roles of IL-23 and Th17 cells in airway inflammation in asthma.

THE BASIS OF IL-23-Th17 CELL AXIS

The original member of IL-17 family cytokines, IL-17A, was reported in 1995 and subsequently 5 cytokines, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F were identified as IL-17 family cytokines (1). IL-17 family cytokines are disulfide-linked homodimeric/heterodimeric proteins that possess a characteristic cystein knot structure (2). IL-17A and IL-17F are mainly produced by a recently identified subpopulation of $CD4^+$ T cells, namely Th17 cells, which seem to be involved in the pathogenesis of a variety of autoimmune diseases (3,4). IL-17A and IL-17F homodimers and IL-17F/IL-17A heterodimer transduce their signals through the receptor composed of IL-17RA and IL17RC (5,6).

IL-23 has been identified as a novel IL-12 family cytokine which is composed of a p19 subunit specific for IL-23 and a p40 subunit shared with IL-12 (7). Despite a structural similarity between IL-12 and IL-23, it is apparent that IL-23, rather than IL-12, plays pathogenic roles in chronic inflammation in a number of disease models, including experimental autoimmune encephalomyelitis, collagen-induced arthritis, psoriasis, and inflammatory bowel diseases (3,4). In addition, a recent study has revealed that IL-23 is crucial for the maintenance of Th17 cells (8). Moreover, McGeachy et al. have shown that IL-23 is required for full acquisition of an effector function of Th17 cells (9). These findings indicate that IL-23-Th17 cell axis plays a key role in the development of inflammatory diseases including autoimmune diseases.

Received on January 27, 2010. Accepted on February 9, 2010.

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Keywords: Asthma, Eosinophils, Neutrophils, IL-17, IL-23, Th17 cells

ROLES OF IL-23-Th17 CELL AXIS IN NEUTROPHILIC INFLAMMATION IN THE AIRWAYS OF ASTHMA

While it is well established that pathognomonic features of asthma including intense eosinophilic infiltration, airway remodeling, and airway hyperresponsiveness (AHR) are mediated by Th2 cytokines such as IL-4, IL-5, and IL-13 from antigen-specific Th2 cells and inflammatory mediators from activated mast cells (10-12), several lines of evidence suggest that IL-17A and IL-17F are also involved in antigen-induced neutrophil infiltration in murine asthma models (13,14). It has also been shown that IL-17A is expressed in the airways of asthmatic patients and its expression is correlated with the severity of asthma (15-17). IL-17A has also been shown to stimulate bronchial fibroblasts, epithelial cells, and smooth muscle cells and induce the expression of a variety of cytokines and chemokines, which are important for granulopoiesis and neutrophil recruitment (18). The ability of IL-17A to evoke migration of neutrophils makes it likely that IL-17A is involved in severe asthma, of which neutrophil infiltration is one of the hallmarks (15-17). Moreover, it has recently been shown that Th17 cell-mediated neutrophilic airway inflammation is steroid-resistant (19). Furthermore, others and we have demonstrated that IL-23 p19 mRNA is induced upon antigen inhalation in the lung of antigen-sensitized mice (20,21). We have also shown that the enforced expression of IL-23 in the lung or the transfer of antigen-specific Th17 cells enhances antigen-induced neutrophil recruitment into the airways (21). These findings suggest that IL-23-Th17 cell axis plays crucial roles in causing neutrophilic airway inflammation especially in severe asthma. Further studies identifying the cellular and molecular targets of IL-23-Th17 cell axis in the induction of neutrophilic airway inflammation could help us to develop a novel therapeutic approach for severe asthma.

ROLES OF IL-23-Th17 CELL AXIS IN EOSINOPHILIC INFLAMMATION IN THE AIRWAYS OF ASTHMA

Recently, we have shown that the administration of anti-p19 antibody, which neutralizes the bioactivity of IL-23 but not of IL-12, attenuates not only antigen-induced neutrophil recruitment but also antigen-induced eosinophil recruitment into the airways (21). The administration of anti-p19 antibody also decreases antigen-induced Th2 cytokine production in the airways (21). In addition, Haworth et al. have shown that resolvin E1, an endogenous lipid mediator, inhibits eosinophhilic airway inflammation by suppressing the expression of IL-23 in the lung (22). Moreover, we have shown that enforced expression of IL-23 in the lung enhances not only antigen-induced IL-17A production and neutrophil recruitment in the airways but also antigen-induced Th2 cytokine production and eosinophil recruitment in the airways (21). These findings suggest a substantial role of IL-23 in causing eosinophilic inflammation in the airways.

The mechanism underlying IL-23-mediated enhancement of eosinophilic airway inflammation is still largely unknown. We have shown that although the production of IL-17A is enhanced by the enforced expression of IL-23 in the lung, IL-23-mediated enhancement of eosinophilic airway inflammation is still observed in IL-17A-deficient mice (21). These results are consistent with previous findings that antigen-induced eosinophilic airway inflammation is induced normally in IL-17A-deficient mice (23,24). In addition, it has been demonstrated that IL-17F-deficient mice exhibit rather exacerbated antigen-induced eosinophilic airway inflammation (25). These findings suggest that IL-23 enhances antigen-induced eosinophilic airway inflammation by the mechanism independent of IL-17A and IL-17F. IL-22, an IL-10-related cytokine, is also expressed in $CD4^+$ T cells under Th17-polarizing conditions and mediates IL-23-induced dermal inflammation and hyperplasia of the epidermis in psoriasis (26). The role of IL-22 in IL-23-mediated enhancement of eosinophilic airway inflammation is under investigation in our laboratory.

We have also addressed the role of Th17 cells themselves in the induction of eosinophilic airway inflammation by adoptive transfer experiments (21). Although the transfer of antigen-specific Th17 cells to non-sensitized mice does not provoke antigen-induced eosinophil recruitment into the airways, co-transfer of antigen-specific Th17 cells with antigen-specific Th2 cells significantly enhances Th2 cell-mediated eosinophil recruitment into the airways (21). When antigen-specific Th17 cells are transferred to antigen-sensitized mice in which endogenous antigen-specific Th2 cells are present, Th17 cells significantly enhance antigen-induced eosinophilic airway inflammation (21). Therefore, it is indicated that Th17 cells themselves do not induce eosinophilic airway inflammation but enhance Th2 cell-mediated eosinophilic airway inflammation.

Interestingly, co-transfer of Th17 cells with Th2 cells enhances the expression of eotaxin-1/eotaxin-2 in the lung (21). In addition, the neutralization of eotaxin-1/eotaxin-2 prior to the

inhaled antigen challenge decreases the eosinophil recruitment into the airways of the mice transferred with a combination of Th2 cells and Th17 cells (21). These findings suggest that Th17 cells may enhance eosinophilic airway inflammation by up-regulating the expression of eotaxin-1/eotaxin-2. In this regard, it has been demonstrated that STAT6 and NF-κB synergistically induce eotaxin expression in fibroblasts and epithelial cells (27). Because Th17 cells produce TNF-α (8), which activates NF-κB pathways, it is plausible that the induction of eotaxin expression by the co-activation of Th2 cells and Th17 cells is mediated by the synergistic effect of IL-4/IL-13-STAT6 pathway and TNF-α-NF-κB pathway. This notion is consistent with a recent report showing the efficacy of TNF-α neutralization by etanercept on severe asthma (28).

Pathophysiological situations in which IL-23-Th17 cell axis plays a crucial role in asthmatic patients remain unclear. Importantly, it has been demonstrated that antigen-presenting cells including DCs produce IL-23 upon a variety of stimuli such as TNF-α, CD40L, LPS, and CpG-ODN. IL-23 is also induced in the lung upon viral or bacterial infection. Thus, IL-23-Th17 cell axis may be involved in the exacerbation of asthmatics by viral or bacterial infection. In addition, it has been reported that the engagement of Dectin-1 by fungal component β-glucan activates DCs to produce IL-23 (29,30). Therefore, IL-23-Th17 cell axis may also be involved in immune responses in allergic bronchopulmonary aspergillosis (ABPA).

In conclusion, IL-23 and Th17 cells are involved not only in causing antigen-induced neutrophil recruitment into the airways but also in the enhancement of Th2 cell-mediated eosinophil recruitment into the airways. Although further studies are required to address the molecular mechanisms of IL-23- and Th17 cell-mediated enhancement of allergic airway inflammation, our results raise the possibility that IL-23 and/or Th17 cells could be a novel therapeutic target for severe asthma.

ACKNOWLEDGEMENTS

This work was supported in part by Grants-in-Aids for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, the Japanese Government and by Global COE Program (Global Center for Education and Research in Immune System Regulation and Treatment), MEXT, Japan.

CONFLICTS OF INTEREST

The author have no financial conflict of interest.

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