Regulation of Th2 and Th17 Cell Responses in Allergic Airway Inflammation

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1. Introduction

Asthma is a heterogeneous disease of the lung and the airway characterized by distinct symptoms such as airway hyper-responsiveness, mucus production, infiltration of inflammatory granulocytes and short-of-breath which could be life-threatening[1,2]. This disease has markedly increased over past several decades and became one of the major global health problems affecting approximately 300 million people worldwide[1]. Asthma can be categorized into allergic and non-allergic asthma based on the types of triggering stimuli[3]. Allergic asthma is a common form of asthma caused by sensitization against allergens such as pollen, house dust mites, fur dander from pet or fungi whereas non-allergic asthma is caused by irritants such as tobacco smoke, ozone, diesel exhaust particles or air-borne virus[1,4]. While allergic asthma has been considered to be Th2-mediated inflammation, recent advances unveiled a critical role for Th17 cells in allergic asthma, particularly neutrophilic asthma, which is known to be steroid-resistant. Hence, the pathogenesis of allergic asthma is becoming complex; however, understanding such complexity will lead to the development of novel diagnostic and therapeutic approaches in humans.

2. Th2 and Th17 cells in allergic asthma

Allergic asthma has been considered to be mediated by Th2 cells; however, recent studies uncovered the involvement of Th17 cells as an additional critical contributor in the pathogenesis of allergic asthma in animal models and in humans[5]. Th2 cells mediate eosinophilic asthma by secreting type 2 cytokines such as IL-4, IL-5, IL-9 and IL-13. These cytokines induce B cell isotype switching to IgE (IL-4), recruit eosinophils (IL-5) and

mast cells (IL-9, IL-13) into the lung and the airway, induce goblet cell hyperplasia and tissue remodeling (IL-13) leading to airway hyper-responsiveness (AHR)[2,6].

On the other hand, Th17 cells have been regarded as a critical mediator of steroid-resistant neutrophilic asthma[7-9]. Elevated levels of IL-17A were observed in the lung from patients with asthma, which was positively correlated with neutrophilic inflammation, increased AHR and steroid-resistant type of severe asthma[10]. A mixed Th2 and Th17 cell response in the airways has been associated with severity of allergic asthma[9,11]. IL-17A stimulates airway epithelial cells to secrete chemokines CXCL1 and CXCL8 which in turn recruit neutrophils[12]. In addition, IL-17A causes airway remodeling via upregulation of α-smooth muscle actin in the fibroblast[13]. Hence, Th2 cells and Th17 cells exert non-redundant pathogenic roles during the development of allergic asthma by inducing eosinophilic and neutrophilic inflammation, respectively.

3. Lessons from clinical and preclinical studies targeting type 2 or type 17 cytokines

Since Th2 and Th17 cell responses play critical and non-redundant roles in the pathogenesis of allergic asthma, there have been a number of attempts to block either pathway in animal models as well as in humans[14]. For instance, anti-IL-4Rα mAb which blocks both IL-4 and IL-13 signaling was clinically tested and found to be ineffective in ameliorating an established allergic asthma[15,16] whereas anti-IL-13 mAb and anti-IL-5 mAb were found to exert limited beneficial effects in asthmatic patients[17-20]. More recently, anti-IL-17RA mAb was clinically tested, but also found to be ineffective in human subjects with moderate to severe asthma[21].

In this context, Choy et al. has recently shown that administration of antibodies to IL-4 and IL-13 increased pulmonary Th17 cell responses and neutrophilic inflammation, suggesting that blockade of Th2 cells resulted in a robust Th17 cell-mediated inflammation in the lung. Importantly, they also showed that co-administration of anti-IL-13 and anti-IL-17A inhibited both eosinophilic and neutrophilic inflammation in the lung in animal models of allergic asthma[22]. This implies that simultaneous targeting of both Th2 and Th17 cell responses would be a promising strategy for the treatment of allergic asthma, while targeting either pathway alone might be ineffective due to the activation of the other pathway. Supporting this notion, GATA-3 and IL-13 are shown to inhibit Th17 cell differentiation[23,24]. Hence, combined blockade of both Th2 cell and Th17 cell pathways might be considered to achieve therapeutic benefits in controlling asthma without adverse effects.

4. Transcription factors that potentially regulate both Th2 and Th17 cells

In search for targets that control both Th2 and Th17 cell differentiation and/or maintenance, our previous study examined if blockade of STAT3 inhibits both Th2 and Th17 cell responses in the airway since the activation of STAT3 is indispensable for Th17 cell differentiation[25,26], and STAT3 has been recently shown to be required for optimal Th2 cell differentiation[27]. Although STAT3-deficient T cells exhibited reduced Th2 cell and Th17 cell differentiation in the bronchial lymph nodes, they showed more robust Th2 cell responses in the airway compared with STAT3-sufficient T cells, suggesting that blockade of STAT3 might increase Th2 cell responses in the airway[28].

Transcription factor RORγt is required and sufficient for Th17 cell differentiation, and RORγt-deficient T cells failed to become Th17 cells[29]. Unlike STAT3-deficient T cells, our recent study showed a consistent reduction of Th2 cell responses in the airway of RORγt-deficient T cells[30]. Consistently, pharmacological inhibition of RORγt also inhibited Th2 cell as well as Th17 cell responses in the airway in wild-type mice in an IFNγ-independent and T cell-intrinsic manner. Based on these findings, we propose that targeting RORγt would be beneficial for the treatment of Th2 cell-mediated eosinophilic asthma as well as Th17 cell-mediated neutrophilic asthma.

5. Concluding remarks

While mild asthma is relatively well controlled by available treatment in humans, there is an urgent need in the development of therapeutics for severe form of asthma. Lessons from past decades demonstrate that simultaneous targeting of both type 2 and type 17 inflammation is a promising approach for severe asthma, which might be achieved by combinatorial treatment with type 2 and type 17 inhibitors, or by targeting pathways that control both type 2 and 17 inflammations in vivo.

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