

REVIEW

Role of Anti-inflammatory Cytokines IL-35 and IL-37 in Asthma

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Abstract—Asthma is a chronic airway inflammation that is characterized by intense eosinophil infiltrates, mucus hypersecretion, airway remodeling, and airway hyperresponsiveness. Interleukin (IL)-35 and IL-37 are two cytokines with anti-inflammatory effects found in immune response. Recent findings suggested that expressions of IL-35 and IL-37 are abnormal in asthma. Functional analysis further confirmed the important roles of them in the pathogenesis of asthma. The present study reviewed the updated evidence indicating the roles of IL-35 and IL-37 in asthma. Hopefully, the information obtained may lead to a better understanding of the pathogenesis of the disease.

KEY WORDS: IL-35; IL-37; asthma.

INTRODUCTION

Asthma is a chronic airway inflammation that is characterized by infiltration of many inflammatory cells, such as mast cells, eosinophils, lymphocytes, basophils, and monocytes, as well as mucus hypersecretion, airway remodeling, and airway hyperresponsiveness (AHR) [1, 2]. These pathognomonic features are mediated mainly by antigen-specific CD4⁺ T helper type 2 (Th2) cells and their cytokines such as interleukin (IL)-4, IL-5, and IL-13 [1, 3]. These inflammatory cytokines are able to induce, prolong, and amplify the inflammatory response by promoting the generation of allergy-specific immunoglobulin E (IgE); promoting recruitment, growth, and differentiation of eosinophils; and directly causing AHR [4, 5]. The other CD4⁺ Th effector subsets, such as Th1 and Th17, also perform significantly in this disease [6]. Th1 cells can exacerbate allergic symptoms and asthma, and expression

of interferon (IFN)- γ is related to antigen-induced AHR and eosinophilic infiltration [7]. Moreover, Th17 cells correlate with neutrophilic airway inflammation and are resistant to corticosteroid treatment in moderate-to-severe asthmatics [8]. Apart from CD4⁺ T cells, CD8⁺ T cells (Tc) are also involved in the regulation of allergic inflammation and AHR [9, 10]. CD8⁺ T cells are classified as Tc1, Tc2, or Tc17 cells according to their distinct cytokine secretion patterns. Tc1 and Tc2 cell subsets mainly produce IFN- γ and IL-4, respectively, while Tc17 cells produce IL-17, IL-21, and IL-22 [11]. Regulatory T (Treg) cells suppress the development of allergy through several mechanisms, such as inhibition of other effector Th1, Th2, and Th17 cells; inhibition of eosinophils, mast cells, basophils, and inflammatory dendritic cells; or inhibition of inflammatory cell migration to tissues [12]. Innate lymphoid cells (ILCs) are a complex and heterogeneous group of lymphoid cells implicated in innate immunity and tissue remodeling [13]. In recent years, ILCs have been divided into different functional subsets: group 1 ILC includes natural killer (NK) and other interferon (IFN)- γ -producing ILCs; group 2 ILCs (ILCs2) includes cells that produce type 2 cytokines (IL-4, IL-5, IL-9, IL-13); and group 3 ILCs produces IL-17 and/or IL-22. ILCs are key players in the pathogenesis of asthma. ILCs do not express antigen receptors but react

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promptly to “danger signals” from inflamed tissues and generate an array of cytokines that direct the ensuing immune response [14]. The role of ILCs in asthma may be different according to distinct asthma phenotypes. ILC2s may be important for initiation of adaptive immune responses in inhaled allergen-driven AHR, but may also function independently of adaptive immunity, mediating influenza-induced AHR. ILC2s are also able to contribute to resolution of lung inflammation *via* their synthesis of amphiregulin. Obesity-induced asthma correlates with expansion of IL-17A-producing ILC3s in the lungs. Furthermore, ILCs might contribute to steroid-resistant asthma [14].

IL-35 is the newest member of the IL-12 family. The IL-12 cytokine family contains IL-12, IL-23, IL-27, and IL-35. They are all composed of α chain (P19, P28, or P35) and β chain (P40 or Epstein–Barr virus-induced 3, EBI3) [15]. IL-35 is a heterodimer composed of EBI3 and P35, signaling through the receptors GP130 and IL-12R β 2, or IL-27R α and IL-12R β 2 [16, 17]. The structure of IL-35 is homology to that of IL-12 because they have same α chain P35, and also similar to that of IL-27 due to their same β chain EBI3 [18, 19]. However, different from the other IL-12 family members, IL-35 is highly expressed on non-stimulated mouse Treg cells and stimulated human Treg cells but not detected in non-stimulated human Treg cells [20, 21]. It can be up-regulated in human non-T cells including microvascular endothelial cells, aortic smooth muscle cells, and epithelial cells after stimulation with tumor necrosis factor (TNF)- α , IFN- β , and IL-1 β [22].

IL-37, formerly named IL-1 F7, IL-37b, is a newly identified member of the IL-1 family [23, 24]. There are five different splice variants of IL-37 termed IL-37a–e, by which IL-37a, b, and d are recognized as the functional forms of IL-37. IL-37b is the largest isoform and is encoded by five of the six exons spanning the *IL-37* gene. None of the isoforms contain a typical signal peptide, but the IL-37a isoform has a unique N terminus encoded by exon 3 [25], and the short isoforms IL-37c, IL-37d, and IL-37e lack exon 4, exon 2, and both exons, respectively. The precursor form is a 30 kDa molecular mass protein that shares critical amino acid residues with IL-18 [26]. IL-37 has been identified in diverse human tissues, including the skin, tonsils, esophagus, placenta, breast, prostate, and colon [27]. It can be induced by several toll-like receptor (TLR) ligands and pro-inflammatory cytokines such as IL-1 β , TNF- α , and IFN- γ in peripheral blood mononuclear cells (PBMCs) and dendritic cells (DCs) [28]. IL-37 translocates to the nucleus and down-regulates lipopolysaccharide (LPS)-induced cytokines. The nuclear translocation of

IL-37 requires caspase-1 activity as evidenced by caspase-1 inhibitors [29] or by mutation of the caspase-1 recognition aspartic acid in the IL-37 precursor [30]. IL-37 exerts anti-inflammatory effects *via* inhibiting innate immune responses through attenuating the generation of inflammatory cytokines induced by TLR ligands, IL-1, and TNF [29, 31]. Consequently, it is possible that IL-37 may act as a cytokine with both intracellular and extracellular functionalities.

IL-1 is a central mediator of innate immunity and inflammation. The IL-1 family comprises seven ligands with agonist activity (IL-1 α , β , IL-18, IL-33, and IL-36 α , β , γ), three receptor antagonists (IL-1Ra, IL-36Ra, and IL-38), and an anti-inflammatory cytokine (IL-37). Members of the IL-1 receptor (IL-1R) family include six receptor chains forming four signaling receptor complexes, two decoy receptors (IL-1R2 and IL-18BP), and two negative regulators (TIR8 or SIGIRR, and IL-1RAcPb). A tight regulation through receptor antagonists, decoy receptors, and signaling inhibitors ensures a balance between amplification of innate immunity and uncontrolled inflammation. IL-33 is a cytokine mainly involved in type 2 immunity and inflammation. Its main effects are on innate and adaptive cells, including innate lymphoid cell-2 (ILC2) and Th cells, and alternatively activated M2-polarized macrophages. IL-33 is a driver of type 2 inflammatory conditions such as asthma, and plays a key role in models of allergic lung inflammation *via* mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF- κ B) signaling pathway [32, 33]. Using a mouse model of LPS-induced acute inflammation, Sha *et al.* found that administration of IL-35 inhibited leukocyte adhesion to the endothelium in the vessels of the lung and cremaster muscle, and decreased the numbers of inflammatory cells in bronchoalveolar lavage fluid (BALF). Mechanistically, IL-35 suppressed the LPS-induced elevation of endothelial cell adhesion molecule VCAM-1 *via* IL-35 receptors gp130 and IL-12R β 2 through suppression of the mitogen-activated protein kinase (MAPK) signaling pathway [34]. Patients with allergic rhinitis reported decreased expression of IL-37, and IL-37 was negatively related to Th2 cytokines. Interestingly, IL-37 down-regulated Th2 cytokine expression through MAPK pathway [35]. Therefore, IL-33 may encounter IL-35 and IL-37, dysregulating Th2 immunity and inflammation partly *via* MAPK signaling pathway. However, the mechanism has not been clarified. Further studies are needed to discuss this interaction (Fig. 1).

Recent findings suggest that expressions of IL-35 and IL-37 are dysregulated in asthma, and functional analysis

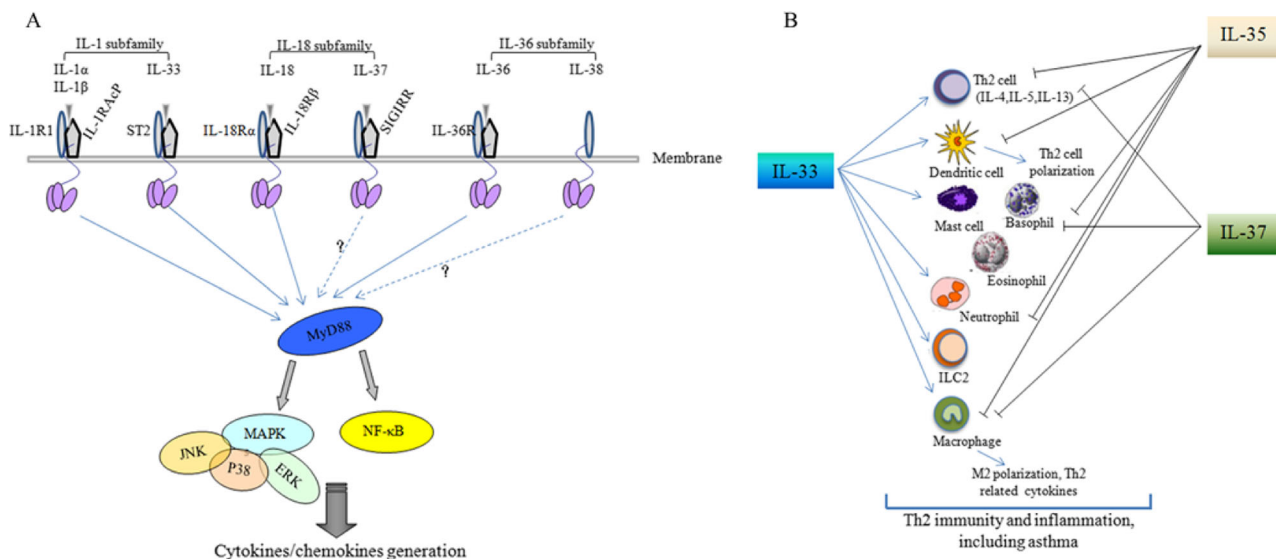


Fig. 1. A model for IL-1 family signaling (a), and IL-33, IL-35, and IL-37 in Th2 immunity (b). **a** IL-1 family is divided into three subfamilies based on the length of the N-terminal propieces. (1) IL-1 subfamily: IL-1 α , IL-1 β , IL-1 receptor antagonist (IL-1Ra), and IL-33. (2) IL-18 subfamily: IL-18 and IL-37. (3) IL-36 subfamily: IL-36 α , IL-36 β , IL-36 γ , and IL-38. The receptor for each IL-1 family cytokine is a heterodimer of the proper or common subunits. IL-1R1, ST2, IL-18R α , and IL-36R are ligand-binding subunits, while IL-1R accessory protein (IL-1RAcP), IL-18R β , and SIGIRR (single immunoglobulin IL-1-related receptor) are signaling subunits. When IL-1 family cytokines bind to the corresponding ligands, they recruit the corresponding signaling receptor subunit and therefore, translocate nuclear factor- (NF-) κ B to the nucleus and activate MAPK (p38, JNK, ERK) pathways. Role of IL-37 and IL-38 in regulation of the signal pathways via mechanisms has not been clearly identified. **b** IL-33 drives type 2 inflammatory conditions including asthma through promoting Th2 cell proliferation and related cytokine generation, as well as Th2 polarization via dendritic cell, or affecting macrophage, neutrophil, mast cell, and eosinophil. By contrast, IL-35 and IL-37 play immunoregulatory roles in Th2 immunity, such as inhibiting Th2-related cytokine production and eosinophil proliferation.

indicates that IL-35 and IL-37 play important roles in the pathogenesis of this disease. The strong association of these cytokines with asthma on multiple levels promotes me to systematically review what had been published recently on the crucial nature of IL-35 and IL-37 in relation to asthma gaining attention for their regulatory capability in asthma. The information obtained may lead to a better understanding of the pathogenesis and development of novel therapeutic strategies for this inflammatory disease.

BIOLOGICAL FUNCTIONS OF IL-35 AND IL-37

Within the CD4⁺ T cell population, IL-35 is produced by resting and activated Treg cells after converting conventional T cells into IL-35-dependent-induced Tregs (iT_{Tr}35) [20]. IL-35 also directly promotes human B cells into IL-10- or IL-35-producing regulatory B cells, attenuating autoimmune and other inflammatory diseases [36]. iT_{Tr}35 cells are strongly inhibitive and stable without the expression of Treg transcription factor forkhead box P3 (Foxp3) [37]. Maximal expression and generation of IL-35

by Treg cells need their interaction with T_H17 cells, which potentiates the inhibitive capacity of Treg cells [38]. Similar to the other regulatory cytokines transforming growth factor (TGF)- β , and IL-10, IL-35 is the major component of the inhibitive repertoire [37]. IL-35 is able to directly inhibit T_H17 cell proliferation in the absence of IL-10 or TGF- β [39]. It has been reported that IL-35 inhibits established collagen-induced arthritis (CIA) in mice by reducing IL-17 synthesis and promoting IFN- γ production [40, 41]. Interestingly, treatment of experimental autoimmune uveitis mice with IL-35 inhibits ocular inflammation and ameliorates symptoms of severe uveitis by suppressing the proliferation of CD4⁺CD25⁺ effector T cells and inhibiting the differentiation of Th17 cells while inducing the expansion of Tregs and regulatory B cells [17] (Fig. 2).

Human PBMCs treated with the neutralizing monoclonal anti-IL-37 are able to increase inflammatory cytokines production, such as IL-1 β , IL-6, and TNF- α [42]. Similarly, PBMCs transfected with siRNA to IL-37 reduce the IL-37 protein abundance, leading to increases in the generation of IL-1 β , IL-6, and TNF- α when stimulated with LPS or Pam3CSK4 [43]. In IL-37 transgenic (IL-37tg)

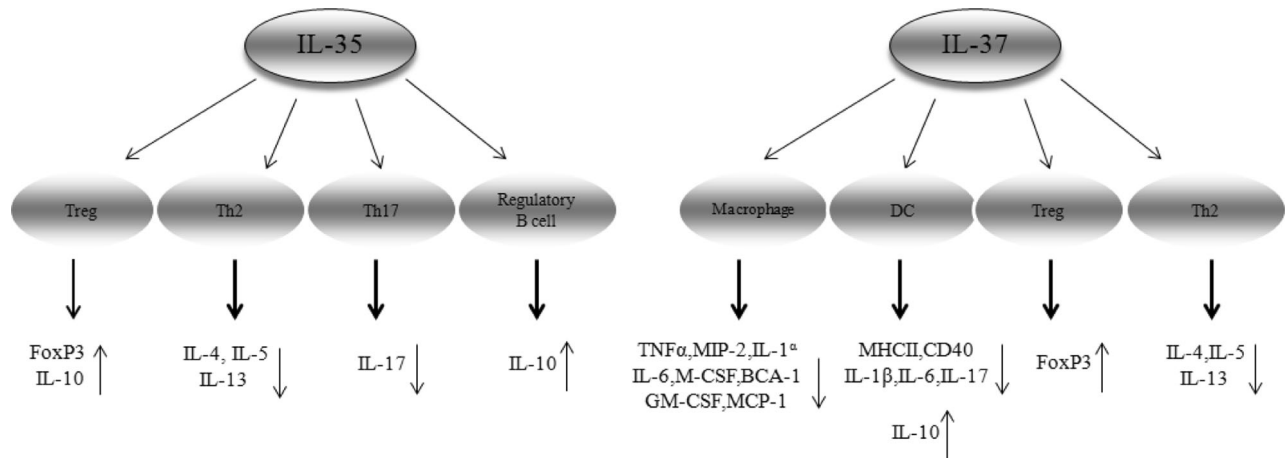


Fig. 2. Role of IL-35 and IL-37 in immune cell function. *Treg* regulatory T cell, *Th2* T helper cell 2, *Th17* T helper cell 17, *DC* dendritic cell.

mice, bone marrow-induced DCs (BMDCs) stimulated with LPS induced a decrease in MHC II and CD40 expression compared with BMDCs from wild-type (TW) mice [44]. 2,4-dinitrofluorobenzene sensitization induced elongated dendritic morphology and elevated MHC II expression in DCs from WT mice skin, whereas these effects were inhibited in DCs from IL-37tg mice skin. Expression of IL-1 β , IL-6, and IL-12 was strongly lower, and expression of IL-10 was significantly higher in BMDCs from IL-37tg mice compared with those from WT mice. When syngeneic T cells, or allogeneic T cells cocultured with BMDCs from WT mice, there was increased proliferation of CD4⁺ and CD8⁺ T cells, but the proliferation was reduced when T cells cocultured with BMDCs from IL-37tg mice. When splenic T cells cocultured with BMDCs from WT mice, there was induced expression of CD4⁺ CD25⁺ Foxp3⁺ Treg cells. Notably, T cells, cocultured with BMDCs from IL-37tg mice, showed enhanced Treg cells [44]. Mouse macrophage RAW cell line can stably express the human IL-37b isoform. IL-37b transfection effectively reduced LPS-stimulated TNF- α , macrophage inflammatory protein-2 (MIP-2), IL-1 α , and IL-6 expression in comparison with mock-transfected RAW cells, and production of macrophage colony-stimulating factor (M-CSF), B-cell-attracting chemokine-1 (BCA-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1 β , monocyte-chemoattractant protein-5 (MCP-5), and IL-23 was considerably reduced in IL-37-treated RAW cells [43]. The epithelial cell line A549 transfected with IL-37b down-regulated constitutive and IL-1 β -induced IL-6 and IL-1 α expression [43]. A549 cells or THP-1 cells transfected with IL-37b displayed

colocalization of IL-37 and Smad3. IL-37b-expressing RAW cells treated with Smad3-specific inhibitor SIS3 can reverse the inhibition of IL-6 and IL-1 α expression, and THP-1 cells treated with SIS3 can up-regulate IL-1 β expression. THP-1 cells were depleted of Smad3 by lentiviral shRNA and then challenged with IL-37, showing with reduced expression of IL-1 β or LPS induced IL-8 and IL-6 [43]. Collectively, these data suggest that IL-37 plays an anti-inflammatory effects in human PBMCs and mouse BMDCs, and regulates the production of inflammatory components in cell lines partly mediated by Smad3 (Fig. 2).

THE ROLE OF IL-35 AND IL-37 IN ASTHMA

Dysregulated Expression of IL-35 in Asthma

IL-35 protein and mRNA expression levels are reduced in allergic asthmatics compared with healthy controls [45]. The frequencies of Tc2 and Tc17 cells are strongly elevated in patients with asthma. Similarly, plasma concentrations of IL-4 and IL-17 are significantly increased in asthmatic patients, and plasma IL-35 protein level is negatively related to the frequency of IL-4-producing CD8⁺ T (Tc2) cells in patients with allergic asthma [45]. In addition, serum levels of total IgE, IL-4, and eosinophil count are strongly up-regulated in asthmatic patients as compared to those of controls, while the serum level of IFN- γ in asthmatic patients is markedly lower than that in healthy controls [46]. There is an obviously positive correlation between serum IgE and IL-4 levels in asthmatic

patients. By contrast, serum total IgE is negatively related to IFN- γ level. Serum level of IL-35 is down-regulated in asthmatic patients, and serum IL-35 level is inversely related to serum IL-4 level. Interestingly, serum IL-35 is positively related to IFN- γ level [46]. It is notable that Wong *et al.* demonstrated the up-regulation of plasma IL-35 and IL-17 in more severe asthmatic patients than that in controls [47]. Plasma level of IL-35 is negatively related to total IgE level in asthmatic patients. The up-regulation of IL-35 positively correlates with disease severity score (DSS). Actually, IL-35 can reverse the IL-17-dependent allergic airway diseases, and attenuate airway inflammation and IgE production, probably in more severe allergic inflammation [48, 49]. It is possible that up-regulation of IL-35 with positive correlation with DSS in severe allergic asthmatic patients may imply the regulatory role of IL-35 being produced in response to the inflammatory reaction in asthma. Together, available evidence suggests that dysregulated circulating IL-35 could be involved in the pathogenesis of asthma by regulating CD4⁺/CD8⁺ T cells.

IL-35 in the Development of Asthma

When BALB/c mice were treated with ovalbumin (OVA) and then administered intranasally adenovirus expressing IL-35 (AdIL-35), the severity of AHR, numbers of inflammatory cells (eosinophils, lymphocytes, and neutrophils) and levels of IL-4, IL-5, IL-13, and IL-17 in BALF were reduced compared with administration of a control virus [50]. AdIL-35 promoted the numbers of CD4⁺CD25⁺Foxp3⁺ regulatory T cells in the lungs. Histological analysis showed that AdIL-35 suppressed allergic lung tissue inflammation and mucus hypersecretion [50]. In addition, the inflammatory response in lung tissue was strongly inhibited in OVA-induced asthmatic mice when IL-35 was injected intraperitoneally during the allergen sensitization stage, as indicated by the strongly reduced numbers of infiltrated eosinophils, neutrophils, and mononuclear cells, as well as the decreased cytokines IL-5 and IL-13 release in the BALF [51]. Similarly, at the sensitization stage, mice displayed a decrease in AHR, which was indicated by the dampened Penh growth [51]. When asthmatic mice were treated with the neutralizing antibody to Ebi3, which displays an ability to specifically interrupt the activity of IL-35 [16], the regulatory role of IL-35 on infiltrating cells in BALF was reversed [51]. Moreover, Huang *et al.* generated an allergen (major house dust mite allergen, Blo t 5)-specific murine Th2 cell line that produced IL-4, IL-5, IL-10, and IL-13, by which these cells displayed CD44^{high}CD62L⁻ and CD127⁺ (IL-7Ra⁺)

phenotypes, which are characteristics of memory/effector T cells [49]. Adoptive transfer of this Th2 cell line in mice following with intranasal challenges with Blo t 5 can induce a dexamethasone-sensitive eosinophilic airway inflammation, accompanied by increased Th2 cytokines IL-4, IL-5, and IL-13; chemoattractants for polymorphic mononuclear cells (CXCL1/KC and CXCL5/LIX); lymphocytes (CXCL9/MIG, CXCL10/IP-10); and monocyte/macrophages (CCL2/MCP-1), as well as recruitment of lymphocytes and polymorphic mononuclear cells into the lungs [49]. Expressions of Blo t 5-specific IgE and IgG1 were also increased. However, pulmonary delivery of the IL-35 DNA constructs effectively reduced Blo t 5-specific allergic airway inflammation, and intramuscular injection of IL-35 resulted in long-lasting inhibition of circulating Blo t 5-specific and total IgE [49], suggesting that IL-35 is able to suppress the Th2-predominant allergic immune response and AHR in asthma.

After administration of IL-35 in OVA-induced asthmatic mice, there was a significant decrease in the percentage and absolute number of the CD11b⁺CD103⁻ DC subset in the mediastinal lymph node (mLN) and lung [51]. When CD11c⁺ cells were isolated from the mLN of asthmatic mice treated with IL-35 and then cocultured with CD4⁺ T cells, the ability to promote CD4⁺ Th cell proliferation was attenuated, accompanied by a markedly reduced expression of IL-4, IL-5, and IL-13. In addition, adaptively transferring intratracheally these CD11c⁺ cells into WT mice led to a moderately dampened AHR, and less peribronchiolar infiltration and mucus production in the airway, with a lower percentage of IL-4-producing CD4⁺ Th2 cells [51]. The data indicated that administration of IL-35 caused an impaired DC trafficking to the lung and draining mLN, and the reduced CD11c⁺ DC in mLN may be an explanation for the IL-35-mediated suppression airway inflammation. Moreover, Ebi-3-deficient mice showed significantly more macrophages, neutrophils, lymphocytes, and eosinophils in the airway, and higher expression of IL-17 after OVA-LPS sensitization [48]. Similarly, mice lacking p35, the other subunit of IL-35, behaved consistently to Ebi-3-deficient mice, by which these mice developed inflammation and AHR [48]. When Whitehead *et al.* measured expression levels of the two IL-35 subunits in ICOS⁺ and ICOS⁻ Tregs prepared from Foxp3-GFP mice, both subunits were expressed by ICOS⁺ Tregs, whereas neither subunit was expressed by ICOS⁻ Tregs. Interestingly, blood collected from human volunteers indicated that human Tregs that expressed ICOS also expressed both subunits of IL-35. By contrast, ICOS⁻ Tregs expressed very low levels of these

subunits [48]. Therefore, IL-35 production by ICOS⁺ Tregs can inhibit IL-17 production and thereby regulate the pathogenesis of asthma.

Reduced Expression of IL-37 in Asthma

The expression of IL-37 mRNA in asthmatic patients was significantly lower than that observed in healthy controls [52–54]. Serum and induced sputum (IS, sputum mononuclear cells that were stimulated with LPS) IL-37 levels were significantly lower in asthma patients compared to those in healthy controls. Protein expression of IL-37 was decreased in the PBMCs of allergic asthmatic patients compared to that of healthy controls, and was significantly lower in allergic asthmatics following anti-CD3/CD28 stimulation [55]. In addition, expression of proline-serine-threonine phosphatase-interacting protein 2 (PSTPIP2), the neutrophil-associated genes CD93, triggering receptor expressed on myeloid cells 1 (TREM1), and regulator of G-protein signaling 13 (RGS13), were increased in patients with nonallergic asthma as compared to those in asthmatic patients [54]. Elevation of PSTPIP2 was not related to reduced asthma symptoms and neutrophilic inflammation in nonallergic asthma patients [54]. CD93 is involved in endothelial cell migration, angiogenesis, leukocyte extravasation, clearance of apoptotic cells, innate immunity, and airway remodeling. It was identical to the C1q receptor and may potentially be implicated in uptake of particles *via* dendritic cells [56, 57]. Sigari *et al.* [58] showed higher serum level of CD93 in patients with asthma exacerbation compared with that in healthy controls, and serum level of CD93 significantly reduced with treatment of asthma attack. TREM1 and RGS13 are both mediators of neutrophil-driven inflammation [59]. Plasma level of TREM1 was higher in asthma bronchiale patients compared with that in healthy controls, by which patients with exacerbated asthma bronchiale reported higher level of TREM1 compared with nonexacerbated asthma bronchiale patients, patients with respiratory tract obstruction than those without obstruction, respectively. The level of TREM1 correlated with number of leucocytes, and absolute number of neutrophils [60]. In a murine model of fungal allergic airway disease, whole lung TREM1 level was increased [61]. This mice model treated with TREM1 exhibited significantly higher AHR following methacholine challenge compared with controls, and whole lung analysis revealed markedly higher amounts of fungal material and increased chemokines CCL17 and

CCL22, suggesting that these inflammatory genes may correlate with asthma but the clear mechanisms of them need to be discussed in the future. In addition, expression of IL-37 was related to these inflammatory components. These data indicated that IL-37 could be an important cytokine in the control of asthma.

IL-37 in the Development of Asthma

It has been found that LPS-stimulated sputum cells from asthma patients generated higher levels of IL-1 β , IL-6, and TNF- α than those from healthy controls [53]. On the contrary, adding IL-37 inhibited TNF- α , IL-1 β , and IL-6 production in IS cells. Similarly, stimulating IS CD4⁺ T cells in the presence of IL-37 significantly suppressed IL-17 production both in asthma patients and healthy controls, but IL-37 effect on IL-17 was more pronounced in patients than that in controls, suggesting that IL-37 may suppress the production of inflammatory cytokines and therefore, plays a negative role in asthma [53]. In asthmatic mice, administration of IL-37 significantly down-regulated the airway inflammation evidenced by diminished eosinophil numbers in BAL and airway tissue, reduced goblet cell hyperplasia as indicated by significantly diminished epithelial basement membrane, and considerably improved AHR [52, 55]. Application of IL-37 down-regulated not only the generation of cytokines attributed to innate immune cells such as IL-6 or IL-12p70 but also the Th2-related cytokines IL-4, IL-5, and IL-13. These data indicated that IL-37 not only acts as a negative regulator of innate immune responses but also has anti-inflammatory properties on an allergic immune response in the airways. It has been shown that IL-37 can bind to IL-18R α , a subunit of the heterodimeric IL-18R [62]. When IL-18R α -deficient mice were treated with OVA, deficiency for IL-18R α completely prevented the beneficial effects of IL-37 on experimental allergic asthma, where IL-37 treatment failed to reduce allergic airway inflammation and goblet cell hyperplasia [52, 55]. Similarly, administration of IL-37 to SIGIRR/IL-1R8-deficient mice treated with OVA did not lead to reduced infiltration of eosinophils into airway tissue and BAL, and had no effect on goblet cell hyperplasia. On the contrary, phosphate buffer saline-treated controls developed experimental allergic asthma as characterized by allergic airway inflammation and goblet cell metaplasia [52, 55]. Collectively, these data suggest a mode of action of IL-37

that involves binding to IL-18R α and subsequent heterodimerization with or activation of SIGIRR/IL-1R8, therefore, mediating the negative effects on allergic airway inflammation and formation of asthma.

CONCLUSION

Recent findings have revealed the therapeutic potential of IL-35 and IL-37 in inflammatory diseases. In type 1 diabetes (T1D) patients and animal models, expression of IL-35 was reduced compared with that in controls [63], whereas IL-35 administration effectively both prevented development of, and counteracted established T1D by induction of Eos expression and IL-35 production in Treg cells, reversing established hyperglycemia in T1D mice. Rheumatoid arthritis (RA) patients showed significantly lower serum levels of IL-35 compared with healthy controls, and the CIA mice model treated with IL-35 decreased the articular index, alleviated arthritis symptoms, and reduced the synovial tissue inflammation [64]. In addition, active RA patients showed higher IL-37 levels compared with patients with inactive RA and healthy controls [65]. On the contrary, IL-17 and IL-17-driving cytokine production were markedly reduced in synovium and joint cells from CIA mice receiving injection of IL-37. ApoE-deficient diabetic mice injected with IL-37 showed significantly less calcification areas detected by both von Kossa and Alizarin Red staining, and much smaller plaque size of the atherosclerotic lesions and lower plaque vulnerability scores detected by hematoxylin-eosin staining in the aorta root [66]. Collectively, these data suggest the potential therapeutic modality using IL-35 and IL-37 in inflammatory diseases.

Evaluating the important roles of IL-35 and IL-37 in regulating CD4⁺ and CD8⁺ T cells, DCs began to shed an interesting light on the understanding of immune-pathologic mechanism in asthma. Dysregulated IL-35 and IL-37 are observed in both asthma patients and mice models. In addition, functional analysis has showed that IL-35 deficiency or blocking IL-37 in asthmatic mice demonstrated impaired disease development and dampened airway inflammation. Since decreased expression of IL-35 and IL-37 correlates with reduced susceptibility for asthma, an adequate manipulation of IL-35 and IL-37 pathway might be critical for regulating normal immune responses. With the advent of more advanced technology and emergence of more elegant studies in the future, the enhanced understanding of the molecular and cellular

targets of IL-35 and IL-37 will be indeed helpful to interpret the pathogenesis of this disease correlated with IL-35 and IL-37.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest. The author declares that she has no conflict of interest.

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