

IL-25 in allergic inflammation

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Funding information

Ministry of Science and Technology of China

Summary

IL-25, also known as IL-17E, is a member of the IL-17 cytokine family mostly produced by epithelial cells and innate immune cells. After binding to the IL-17RB/IL-17RA complex, IL-25 induces downstream signaling responses in epithelial cells and type 2 lymphocytes, which initiates, propagates, and sustains type 2 immunity. The function of IL-25 in allergic diseases such as asthma has been well established, and now also is extended to diseases such as inflammatory bowel disease and cancer. This review summarizes the literature on IL-25 and discusses the unsolved questions. Our knowledge on IL-25 will pave the pathway for targeting this cytokine in inflammatory diseases.

KEYWORDS

allergic diseases, cell source, cell target, cytokines, IL-25, IL-25-mediated diseases

1 | INTRODUCTION

Cytokines constitutes a complex networking important in initiating and shaping of inflammatory responses. There has been progress in the past several years in understanding the initiation and development of type 2 immune pathology, among which allergic asthma is best studied. Asthma is characterized by several changes including local infiltration by Th2 cells and eosinophils, the physiological and structural changes in the airway, leading to mucus hyperproduction and airway hyperresponsiveness (AHR).¹ Th2 cells play central roles in the pathogenesis of allergic asthma disease in response to environmental allergens.

IL-17 family cytokine members have recently emerged as key mediators in both acute and chronic inflammatory responses.² Since the discovery of IL-17A (also called IL-17 or CTLA8), other members of this family IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F have been identified based on amino acid sequence homology.^{3–6} IL-17 and IL-17F are well characterized to critically promote tissue inflammation and play important roles in autoimmune responses.^{7,8} IL-17C is also upregulated after bacterial and fungal infection and in autoimmune diseases and play important roles in modulating inflammatory responses.^{9–14}

IL-25, initially defined as a Th2 cell-derived cytokine,¹⁵ is unique in its structure and function. IL-25 only shares 16–20% amino acid sequence identity with that of IL-17,^{15,16} suggesting distinct function. During the past years, multiple studies have showed IL-25 function was mainly related to the pathogenesis of allergic^{17–24} and colitic diseases²⁵ and immunity against worm infection.^{26–28} Multiple cellular sources including lung and colon epithelial cell,^{22,25} alveolar macrophage,¹⁹ mast cell,²⁹ eosinophil, and basophil²³ were identified. IL-17RB, the specific binding receptor for IL-25, also called EVI27 or IL17 receptor homolog 1 (IL-17Rh1), is a 56-kDa single transmembrane protein show homology to IL-17 receptor A. IL-17RB is broadly expressed in epithelial cells of multiple tissues, but only restricted to type 2 cells in the lymphoid system.^{16,22,30–32} Over the past decade, IL-25 has been demonstrated to play important roles in innate and adaptive immune responses, especially the allergic diseases.

2 | IL-25 IN ALLERGIC ASTHMA

2.1 | Function

The pulmonary allergic disease is result from dysregulated type 2 immunity and characterized by several changes including lung epithelial cell hyperplasia, the local infiltration of Th2 cells and eosinophils, as well as physiological and structural changes leading to mucus

hyperproduction and AHR.¹ In 2001, Fort et al. and Lee et al. found that IL-25 intraperitoneal injection or overexpressing human or mouse IL-25 in vivo led to typical type 2-biased immune reactions, including increased expression of IL-4, IL-5, and IL-13 in multiple tissues, increased serum IgE and IgG, and recruitment of eosinophils in lung and stomach.^{15,16,33,34} These observations raised the possibility that IL-25 may be unique in the IL-17 family to promote type 2 immunity. In support of this idea, intranasal injection of IL-25 increased eotaxin mRNA expression, production of IL-4, IL-5, and IL-13, eosinophil infiltration in the lung, and asthma features such as the epithelial cell hyperplasia and mucus hypersecretion.¹⁸ In another study, IL-25 treatment caused eosinophilic inflammation, mucus hypersecretion, and a progressive increase in the production of type 2 cytokines besides AHR in the lungs, which were abolished in IL-13^{-/-}, IL-4R α ^{-/-}, and STAT6^{-/-} (signal transducer and activator of transcription 6) mice.²⁰

To study the mechanisms underlying IL-25-driven allergic responses, Angkasekwinai et al.²² constructed mice in which mouse IL-25 was transgenically expressed by lung epithelial cells. At 5 months of age, the transgenic mice spontaneously developed phenotypes that were allergy-like, such as eosinophil and CD4⁺ T-cell infiltration, mucus hyperplasia, and epithelial hyperplasia, whereas deficiency in IL-25 reduced the airway inflammation and Th2 cytokine production in an allergen-induced asthma model. IL-25 directly acted on epithelial cells to induce pro-allergic chemokine production. Moreover, IL-17RB was found to be selectively expressed by Th2 cells.²² IL-25 promoted Th2 cell differentiation in an IL-4- and STAT6-dependent manner. In addition, during early T-cell activation, IL-25 potentiated expression of the nuclear factor of activated T cells, c1 and JunB transcription factors, which resulted in upregulated production of initial IL-4 GATA-3, and enhanced Th2 cell differentiation.²²

In line with these findings, Tamachi et al.²¹ also found that inhibition of IL-25 binding by using a soluble IL-25 receptor decreased lung-infiltrating eosinophil and CD4⁺ T cells, and the level of Th2 cytokines. Ballantyne et al. reported that blockade of IL-25 in an OVA-induced allergic asthma model prevented the progression of AHR. What is more, administration of an anti-IL-25 mAb during the sensitization phase resulted in vastly reduced expression levels of IL-5 and IL-13, eosinophil infiltration, goblet cell hyperplasia, and serum IgE secretion,²⁴ resulting in much slower type 2 inflammatory response.

In addition to the findings in mice, IL-25 and its receptor were also found to be expressed in the asthmatic bronchial mucosa upon the allergen provocation.³⁵ In another study, the epithelium-derived IL-25 expression in patients was used to determine the type 2 status in asthma and IL-25-low and IL-25-high subjects showed distinct clinical and pathologic characteristics.³⁶ In terms of virally induced asthma exacerbation, IL-25 expression was enhanced in asthmatic bronchial epithelial cells after RV infection.³⁷ These human data provide evidence for the importance of IL-25 in allergic asthma development.

Thus, IL-25 is a critical factor strongly expressed in allergic airway inflammation, which selectively enhanced Th2 cell responses and potentially provoked human asthma progression.

2.2 | Cell source

IL-25 was first known as a Th2-derived cytokine as its mRNA expression was found in highly differentiated Th2 cells polarized for 3 weeks.¹⁵ Later, IL-25 was found to be produced by bone marrow-derived mast cells upon IgE crosslinking,²⁹ suggesting the involvement of mast cell-derived IL-25 in the regulation of allergic disease. In 2005, Chun-Mi Kang et al.¹⁹ found that alveolar macrophages during particle-induced lung inflammation produced IL-25; these cells play a pivotal role in particle-induced lung inflammation through direct induction of IL-13 and IL-25 production. Moreover, it was also reported human eosinophils and basophils expressed IL-25 transcripts, and activated eosinophils and basophils from normal and atopic subjects secreted bioactive IL-25 protein.²³ Treatment of IL-5 and GM-CSF enhanced the expression of IL-25 by eosinophils, while the expression by basophils could be further upregulated upon IgE crosslinking.

Lung epithelial cells are the first barrier to encounter the allergens and served as important producers of multiple cytokines and chemokines in allergic asthma. When exposed to allergens such as ragweed and fungus *Aspergillus*, *IL25* mRNA expression was upregulated along with several other chemokines,²² suggesting that IL-25 may contribute to the initiation of allergic response. Furthermore, lung-specific IL-25 transgenic mice showed both the airway infiltration such as eosinophils, macrophages, and CD4⁺ T cells in the lung and the pathological alteration, including mucus hyperproduction and epithelial cell hyperplasia.^{21,22}

Taken together, IL-25 produced by multiple cell types proved to be of functional importance, such as eosinophil, basophil, and lung epithelial cells may contribute to the phases of both initiation and progression of allergic disease.

2.3 | Cellular targets

To understand the mechanisms of IL-25 function in type 2 immune responses, it is critical to identify the cellular targets of IL-25. Lung epithelial cells, as the first barrier to allergens, were shown to potentially initiate tissue inflammatory responses mainly by producing a lot of cytokines and chemokines. These cytokines and chemokines were responsible for the recruitment of inflammatory cells and amplification of allergic responses. During allergic airway response, the receptor for IL-25 was shown to be constitutively expressed by lung-resident cells such as lung fibroblast³⁸ and lung epithelial cells,^{22,39} suggesting a direct function of IL-25 on those cells. IL-25 treatment on those cells induced several chemokine expression such as eotaxin, TARC, and MDC, which are essential for recruiting eosinophils and Th2 cells.²² In addition, TSLP, a key factor in allergic inflammation,⁴⁰ was also observed to be upregulated.²² The expression of IL-17RB by human lung fibroblast was found to be further upregulated by TNF- α treatment decreased with TGF- β 1.³⁸ Endothelial cells were also found to be another cell target of IL-25. IL-25R⁺ cells colocalized with CD31⁺ blood vessel endothelial cells in vivo and *IL25r* mRNA was found to be expressed in human vascular endothelial cells in vitro and IL-25 treatment promoted the proliferation of these cells,

along with the increased numbers, and length and area of microvessel structure, signs of angiogenesis.⁴¹ In airway remodeling, IL-25 directly acted on mesenchymal cells to induce collagen secretion and remodeling. Blockade of IL-25 abolished angiogenesis in vivo by defective recruitment of endothelial progenitor cells and delayed neovascularization.⁴²

Several reports indicated Th2 cells as a cellular target of IL-25 in allergic diseases in vivo and Th2 cells are the major producer of cytokines orchestrating allergic reaction.^{20,22,23} CD4⁺ T-cell deficiency inhibited the IL-25-induced allergic airway inflammation.²¹ IL-17RB, the specific receptor for IL-25, was detected in mouse naive CD4 T cells and induced further in differentiated Th2 cells.^{22,43} Not only expressed by Th2 cells, IL-25 may function to promote Th2 differentiation. Naive lymph node cells cultured in the presence of IL-25 enhanced their production of IL-4, IL-5, and IL-13, indicating that IL-25 promoted Th2 responses directly. Furthermore, during allergen-induced allergic airway inflammation, neutralization of endogenous IL-25 led to the attenuated antigen-specific Th2 response,²² indicating the potential role of IL-25 in regulating type 2 helper T-cell priming.

IL-17RB mRNA was upregulated in human circulating Th2-biased memory cells⁴⁴ and activated Th2 memory cells, suggesting a potential function of IL-25 on T cells. Wang et al. also showed that when activated with thymic stroma lymphopoietin-treated dendritic cells (TSLP-DCs), IL-25 treatment on human CRTH2⁺ memory cells promoted T-cell expansion and Th2 cytokine production, suggesting the function of IL-25 in inducing further polarization of memory Th2 cells.^{43,44} Further study provided the evidence that upregulation of Th2 cytokine production by TSLP-DC was independent of IL-4.²³

However, murine Th2 differentiation induced by IL-25 is dependent on early IL-4 expression.²² Treatment of IL-25 on IL-4-deficient naive T cells or with antagonistic anti-IL-4 antibody abolished the effect that IL-25 treatment upregulated the early expression of *Il4* during naive T-cell polarization, followed by enhanced Th2 cytokine production such as IL-5 and IL-13 in 3 days, suggesting that endogenous IL-4 is required for IL-25-mediated enhancement of Th2 differentiation. In addition, *Il17rb* mRNA expression was sustained during Th2 differentiation by time-course analysis during T-cell differentiation indicating that IL-25 might also be involved in functional regulation of effector Th2 cells and memory Th2 cells. Thus, CD4⁺ T cells could be a functional cellular target of IL-25 during allergic disease development either by directly influencing naive T-cell differentiation or maintain the effector Th2 cell in expansion.

In addition to Th2, a newly described subset of T-helper cells that could produce high level of IL-9, called Th9, expressed high levels of mRNA for IL-17RB.¹⁷ TGF- β plus IL-4 is a polarizing condition for the generation of Th9, also for the induction of the expression of IL-17RB. IL-25 treatment on Th9 cells enhanced IL-9 secretion. Moreover, transgenic overexpression of IL-17RB in T cells resulted in IL-25-induced IL-9 production, leading to strong allergic responses.⁴⁵

In recent years, more and more studies suggested a new target for IL-25: Group 2 innate lymphoid cells (ILC2). ILC2 cells have an

important role in early innate responses to helminth infection and in the pathophysiology of various allergic inflammatory responses including asthma.^{46,47} Fort et al.¹⁵ first demonstrated that a new type of cells called non-B/non-T cells as the major IL-25 target cells; these novel cells produced IL-4, IL-5, and IL-13 by IL-25 stimulation and were suggested to be mast cells or its precursors or hematopoietic stem cells on the basis of c-Kit expression. Further phenotypic characterization indicated that these IL-25 responder cells did not express any lineage markers but express MHC II and low levels of CD11c. In 2010, the identity of this mysterious cell type was revealed^{48–50} to be natural helper cells found in adipose tissues of naive mice and characterized as Lin[−]c-Kit⁺Sca-1⁺ cells that could produce large amounts of type 2 cytokines upon stimulation of IL-33.⁴⁸ IL-25 strongly activates these cells together with IL-2.^{48,51} This novel type of lymphocytes is now formally called “ILC2”. Along with the findings in mice, human type 2 ILC population was also observed.^{52,53} In 2011, a population comparable to mouse type 2 ILC was reported in lung and gut, defined as CRTH2⁺CD127⁺CD161⁺. These cells responded to IL-2 plus IL-25 and IL-33 in vitro by producing IL-13 but not IL-17 or IL-22, distinct from RORgt⁺ ILC. These human data further support the idea that ILC2 as one of cell targets of IL-25 contribute to the development of airway inflammation.⁵⁴ In 2015, Huang et al.⁴⁷ demonstrated the effects of IL-25 on the induction and activation of ILC2 cells and found that in the lungs, IL-25 alone potently induces Lin[−]IL-33R⁺KLRG1^{hi}ILC2 cells, which are IL-7R⁺ and cannot induced by IL-33. IL-25 drives ILC2s to play multiple roles in several diseases, such as atopic dermatitis⁵⁵ and immunity to both helminths and fungi.⁴⁷ Epithelial cell-derived cytokines including IL-25, thymic stromal lymphopoietin (TSLP), and IL-33⁵⁶ mediate allergen-induced type 2 ILC2 activation and development, leading to the secretion of IL-5 and IL-13 and contribute to the pulmonary allergic asthma diseases.⁵⁷ For example, Barlow et al.⁵⁸ showed that IL-25 was potent in provoking IL-13-producing ILC2 cells and airway contraction, although IL-33 showed more potent effect. Martinez-Gonzalez et al.⁵⁹ also reported IL-25 as a strong activator of ILC2 in allergic diseases; even memory-like ILC2 had the responsiveness to IL-25.

Besides the cell types, it was also reported that IL-17RB was also highly expressed on a subset of naive and activated CD4⁺ invariant NKT (iNKT) cells.⁶⁰ Upon stimulation with their ligand, α -galactosylceramide (α -GalCer), IL-17RB⁺ iNKT cells produced high levels of Th2 cytokines that were much increased by IL-25 stimulation. These cells restored AHR in iNKT cell-deficient mice, whereas IL-17RB[−] iNKT cells failed to reconstitute AHR and lung inflammation.⁶⁰ IL-25-activated IL-17RB⁺ NKT cells produced IL-13 predominantly as well as Th2 chemokines CCL17, CCL22, and eosinophil chemotactic factor-L.

In chronic allergen responses, IL-17RB was induced in a myeloid cell population, identified as IL-4⁺CD11b⁺Gr1⁺ cells both in lung and bone marrows.⁶¹ Whether these cells represent natural M2 macrophages remains to be determined.

Altogether, IL-25 may regulate multiple cell types to either initiate the allergic progression through the innate cell types or adaptive CD4⁺ T cells in the production of Th2 cytokines to orchestra the development of allergic disease.

3 | IL-25 IN OTHER DISEASES

3.1 | Infection

IL-25 is pathological in allergic diseases, but protective in several intestinal helminth infection models, consistent to its critical role in type 2 immunity.^{26,27,32} Although in most cases Th2-related cytokines protect against intestinal helminth parasites, effector molecules may exhibit specific effects against a particular parasite.⁶² For example, during *Trichuris muris* infection, IL-25 promoted a Th2 cytokine-dependent immune response and goblet cell hyperplasia, but by contraries, limited the pro-inflammatory cytokine production and chronic inflammation in gastrointestinal tract.²⁷ IL-25-deficient mice failed to expel *Nippostrongylus brasiliensis* efficiently which might be caused probably by impaired Th2 protective immunity and by reduced intestinal smooth muscle and epithelial responses to *N. brasiliensis* infection.^{26,32}

In addition to parasite infection, IL-25 showed pathological effect in *C. rodentium* infection model, in which, *IL25*^{-/-} mice exhibited a slight, but significant improvement in weight and fecal bacteria compared to WT mice.²⁵

3.2 | Autoimmunity

The role of IL-25 in autoimmunity is not clear. A previous study showed that IL-25 inhibited Th17 response in experimental autoimmune encephalomyelitis. IL-25-deficient mice were highly susceptible in this disease, while IL-25 treatment completely suppressed the disease.⁶³ These data indicate the opposing roles of IL-25 and IL-17 in the pathogenesis of organ-specific autoimmunity. However, it is not clear whether IL-25 acts by promoting anti-inflammatory Th2 response.

IL-25 may also play important roles in colonic inflammation. Injection of IL-25 throughout the course of DSS-induced colitis was reported to result in a protective response, associated with reduced inflammation and increased survival.²⁸ However, in a model of oxazolone-induced colitis, IL-25 exhibited pro-inflammatory effect, as neutralizing IL-25 or IL-17RB decreased colitis.⁶⁴ Consistent with the later report, deficiency of IL-25 caused decreased DSS-induced colitis, including decreased colonic inflammation and pathology.²⁵

3.3 | Cancer

The role of IL-25 in tumor pathogenesis is poorly understood. Recent studies indicate that IL-25 could induce cell death in breast cancer cells while non-malignant cells were not affected.⁶⁵ In another study, IL-25 seemed to show a wide anti-tumor effect such as in melanoma, lung, colon, and pancreatic cancers; injection of recombinant IL-25 every other day resulted in significant anti-tumor activity in these tumor models.⁶⁶ On the other hand, IL-25 was recently found to be expressed abundantly in all four major types of human breast cancer patients, and both tumor cells and tumor-infiltrating cells expressed high levels of IL-25.⁶⁷ IL-25 was also highly expressed in

MMTV-PyMT, a highly malignant spontaneous breast tumor model at primary tumor site by tumor-infiltrating CD4⁺ T cells and macrophages, but not in the metastatic lung tissue. Neutralization of IL-25 substantially reduced lung metastasis while not affecting primary tumor growth, which is consistent with the role of Th2 cells in promoting breast cancer metastasis.⁶⁸ Indeed, IL-25 blockade resulted in decreased Th2 cells and macrophages in the primary tumor microenvironment.

4 | IL-17B

IL-17B, a poorly understood cytokine in the IL-17 family, shares the receptor protein IL-17RB with IL-25, which raises whether IL-17B and IL-25 have overlapping or antagonistic function. In mucosal inflammation model, IL-17B and IL-25 were expressed by colon epithelial cells, and the expression is regulated by innate immune activators.^{25,69,70} While deficiency of IL-25 caused decreased DSS-induced colitis, deficiency of IL-17B showed opposing phenotype.²⁵ Further study revealed that when stimulated with IL-25, colon epithelial cells produced IL-6. However, IL-17B did not show this effect and could inhibit the expression of IL-6 induced by IL-25 and high-dose IL-17B even abolished IL-6 expression. IL-17B inhibited IL-25 signaling through inhibiting its ability to bind to IL-17RB and double deficiency of IL-17B and IL-25 reverts a single-deficient animal back to WT phenotype.

This effect is not specific to acute colitis. In *C. rodentium* infection model, IL-17B is protective against *Citrobacter rodentium* infection, while IL-25 showed pathological effect in this model in weight loss and bacterial burden.²⁵ Deletion of both cytokines resulted in a phenotype similar to WT mice. In airway inflammation model, IL-25 strongly promoted allergic airway inflammation, whereas IL-17B restrained Th2 cell responses in the airway. Thus, IL-17B acts as a natural antagonist for IL-25 in multiple systems.²⁵

5 | SIGNAL TRANSDUCTION BY IL-25

In light of the crucial role of IL-25 in multiple diseases, it is important to understand the signaling pathways downstream of IL-25. IL-17RB, as the binding receptor for IL-25, needs to associate with IL-17RA as a signaling complex. Splenocytes from IL-17RB KO and IL-17RA KO mice did not produce IL-5 or IL-13 in response to IL-25 stimulation.^{45,71} Also, Angkasekwinai et al. reported that addition of IL-25 to T cells cultured in Th9-polarizing conditions largely increased IL-9 secretion in wildtype cells but not on IL-17RA-deficient cells, suggesting that IL-17RA is required for the IL-25 effect on IL-9 production in CD4⁺ T cells.¹⁷ Further study showed that when IL-17RA and IL-17RB were both overexpressed in 293T cells, they could be immunoprecipitated as a complex suggesting the indirect binding for IL-25 with IL-17RA. Although IL-17RA does not directly interact with IL-25 in in vitro binding assay, IL-17RA bound to the IL-17RB-IL-25 complex with an affinity of $14.1 \pm 2.4 \mu\text{mol L}^{-1}$.⁷² Mice lacking expression of

IL-17RA and IL-17RB both failed to exhibit IL-25-elicited population expansion of the c-Kit^{int} cells,⁵¹ indicating the lineage negative cells also require IL-17RA for IL-25 signaling. Thus, IL-17RA and IL-17RB form a complex to interact with IL-25 to activate the downstream factors for signal transduction.

Act1, the critical adapter for IL-17RA signaling,⁷³ is also proved to be involved in IL-17RB signaling. CIKS/Act1 was essential for IL-25-mediated allergic airway inflammation.⁷⁴ When the SEFIR domain was deleted in either Act1 or IL-17RB, the interaction between Act1 and IL-17RB was abolished, indicating the homotypic interaction of the SEFIR domain was critical for the recruitment of Act1 to IL-17RB. In vivo, mice lacking Act1 in epithelial cells reduced Th2-associated gene expression upon IL-25 intranasal inhalation and consequently affected the development of pulmonary inflammation.⁷⁵

TRAF6, downstream Act1, is also involved in IL-25 function. Though IL-25 activates ERK, JNK, and p38 by a TRAF6-independent mechanism, this protein is essential for NF- κ B activation.⁷⁶ TRAF6-deficient cells were defective in IL-25 receptor-mediated gene expression such as IL-6, TGF- β , and G-CSF.⁷⁶ IL-17RB possesses TRAF6-binding sites, while IL-17RA lacks a TRAF6-binding site. Moreover, IL-17RB-mediated NF- κ B activation was attenuated when TRAF6-binding motif was mutated in cells expressing IL-17RB.⁷⁶ Therefore, the mechanisms for TRAF6 activation might be different in IL-17RB- and IL-17RA-mediated signaling. The role of TRAF6 for IL-25 signaling was further indicated by several in vivo experiments. In epithelial cells, IL-17RB is known to activate NF- κ B and MAPK pathways through TRAF6⁷⁶ and IL-25 induces PKC ϵ phosphorylation in brain capillary endothelial cells to induce claudin-5, which is important for maintaining the blood brain barrier function.⁷⁷

6 | SUMMARY AND FUTURE PERSPECTIVES

Taken together, IL-25, as a cytokine belongs to IL-17 family, plays pivotal roles in multiple diseases, especially allergic asthma. In response to allergen challenge, IL-25 drives the disease development in both innate and adaptive phases. Several innate immune cell types produce IL-25, including lung epithelial cells such as eosinophils, basophils, mast cells, and alveolar macrophage. As a result, IL-25 signaling in lung epithelium or fibroblast cells promotes the production of pro-allergic chemokines such as eotaxin, TARC, and MDC to recruit the eosinophils and type 2 immune cells. IL-25 also regulates the activation of ILC2 and iNKT cells. In adaptive immunity, IL-25 is involved in the polarization and differentiation of naive T cells to Th2 cells and further contributed to the function of effector Th2 cells. IL-25 thus is a master switch in the allergic response and can be targeted in allergic asthma.

Though IL-25 is well studied in allergic asthma, the function, cellular sources, target cells, and underlying mechanisms need to be further studied in the context of other diseases. This line of studies may unveil novel regulation in the immune and inflammatory responses and offer new strategies for treatment of a wide variety of diseases.

ACKNOWLEDGEMENTS

We thank our colleagues for their scientific contribution to the topic. This work is partially supported by Ministry of Science and Technology of China (2016YFC0906200 to C.D.). C.D. is a Bayer Chair Professor at Tsinghua University. This work was supported by grants from National Natural Science Foundation of China (31570884 to X.W. and C0801 to C.D.) and National Key Research and Development Program of China (2016YFC0906200 to C.D.). C.D. is a Bayer Chair Professor at Tsinghua University.

CONFLICTS OF INTEREST

Miao Xu and Chen Dong prepared the manuscript and there is no conflict interest.

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How to cite this article: Xu M, Dong C. IL-25 in allergic inflammation. *Immunol Rev.* 2017;278:185–191. <https://doi.org/10.1111/imr.12558>