



IL-25: Regulator of Type 2 Inflammation in Allergic Nasal Mucosa

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Abstract

Purpose of review Allergic nasal mucosal inflammation generally refers to the development of allergic rhinitis characterized by IgE-mediated mast cell responses, eosinophil infiltration, and augmented Th2 cytokines/chemokine production in the nasal mucosa. However, due to the complexity of the disease, its detailed mechanism has yet to be fully elucidated. Hence, in this review, we aim to collate the studies of IL-25 pertaining to its role in allergic mucosal inflammation to help drive future research of IL-25 in utilizing it as a potential target in the management of allergic sinonasal diseases.

Recent findings At the turn of the century, interleukin (IL)-25 was discovered as a novel member of the IL-17 cytokine family found to be derived mainly from nasal/airway epithelial cells, Th2 cells, and activated eosinophils. It is found to play a pivotal role in nasal allergic mucosal inflammation as a master regulator of promoting type 2 responses mediated by both Th2 cells and ILC2s, augmenting allergic inflammation. IL-25 is highly bioactive by mainly reacting through IL-25R/IL-17RB which activates a myriad of transcriptional factors including p38 MAPK, NF-κB, STAT 5, and Act1 which contributes to its role in allergic mucosal inflammation.

Summary This review collated results that showed that IL-25 serves as a bridge between the epithelial cells and inflammatory cells in the sinonasal mucosa in promoting type 2 allergic inflammation, as well as between the innate immunity and acquired immunity via the feedback between ILC2s and Th2 cells to amplify and perpetuate allergic inflammation, which indicates IL-25 as a promising target for future biologics development.

Introduction

The mammalian immune responses are generally divided into two major categories: type 1 and type 2. Type 1 responses are mediated by T helper 1 (Th1) and Th17 cells via IFN- γ secretion with IgG in response to bacteria, viruses, fungi, and protozoa invasion, whereas type 2 responses are regulated by T helper 2 (Th2) cells via interleukin (IL)-4, IL-5, and IL-13 secretion with IgE to cope with extracellular parasites and allergic inflammatory diseases [1•].

In nasal allergic mucosal inflammation, the immune response is chronically skewed towards a Th2 inflammatory condition of a non-infectious nature. Features of the inflammation include eosinophils, basophils, mast cells, and T cell infiltration; proinflammatory cytokines (IL-4, IL-5, IL-13) secretion; and immunoglobulin E (IgE)-mediated humoral immune response. Such responses typically occurred when an atopic individual is sensitized to a specific antigen and subsequently get re-exposed to the same antigen in the nasal mucosa [2]. The pathogenesis of the nasal allergic response includes the early-phase responses, late-phase responses, and ongoing inflammation. The early-phase responses are immediate responses to the specific nasal allergen challenge taking place within 5–30 min of exposure. The response is a result of the crosslinking of allergen and

allergen-specific IgE bound to high-affinity IgE receptor Fc ϵ RI on mast cells and basophil surfaces. The crosslinking de-granulates these cells to release mediators like histamine and leukotriene causing mucosal edema rapidly [2, 3•]. The late-phase responses occurred within 6–24 h of exposure and are characterized by the recruitment and activation of effector cells composed of eosinophils, basophils, and Th2 cells. The recruited Th2 cells further release IL-4, which causes serotype switching in B cells to produce IgE; IL-5, an eosinophil growth factor; and IL-13, a trigger of mucus hypersecretion and airway hypersensitivity. In combination, the effects of these factors resulted in damages to the nasal mucosa and perpetuate the inflammation [2, 3].

More recently, it was found that the epithelial cells also participated actively in allergic mucosal inflammation by releasing cytokines and chemokines like RANTES, eotaxin, MCP-4, and thymus- and activation-regulated chemokine (TARC) to facilitate the infiltration of the effector and inflammatory cells [4]. Hence, this finding opens up avenue for the search of the link between the epithelium and the resulting inflammation during allergic inflammation. The mechanisms and pathways leading to allergic inflammation in the nasal mucosa are summarized in Fig. 1.

Discovery of IL-25: a novel member of IL-17 family

IL-25, also known as IL-17E, is a member of the IL-17 cytokine family characterized by a conserved gene sequence that codes for 4–5 cysteines in its C terminus and a variable N terminal coding amino acid sequence of 1–4 cysteines [1]. IL-25 is first described as a Th2-derived cytokine using an IL-4/anti-IL-12 monoclonal antibody polarized murine model in 2001 by Fort et al. It was found that while structurally homologous with IL-17, IL-25's bioactivity differs significantly from other members of IL-17 family, IL-17A, IL-17B, and IL-17C, which typically induce the production of TNF- γ and IL-1 β . The classical IL-17

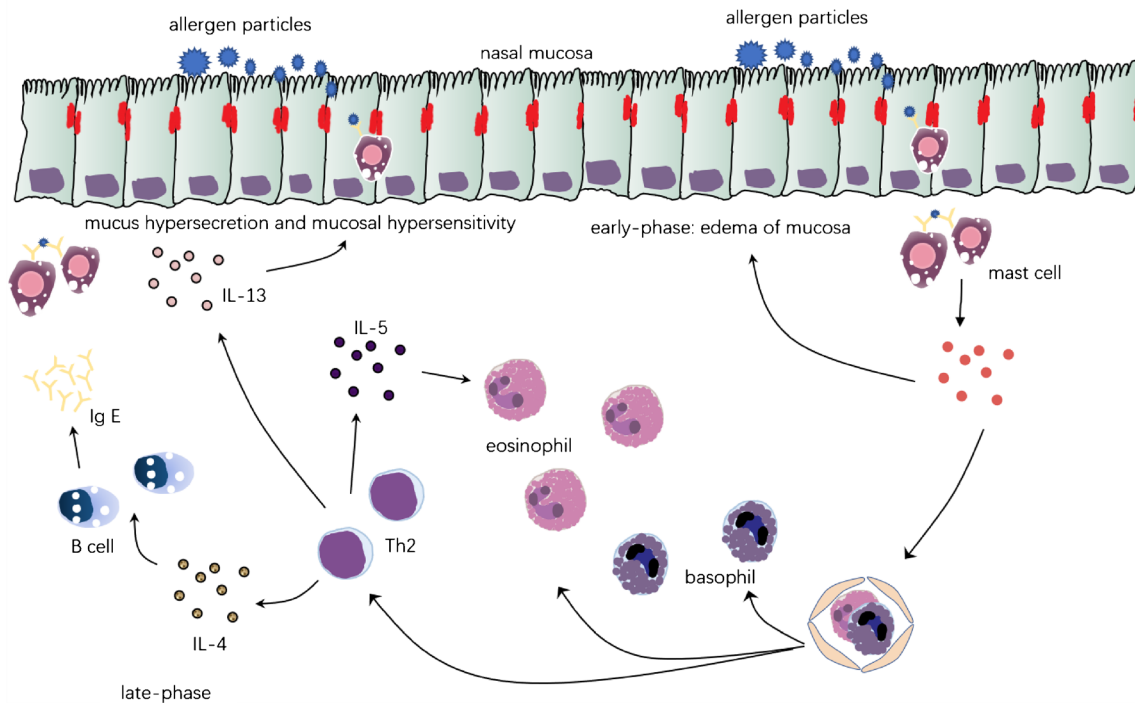
Allergic inflammation of the nasal mucosa

Fig. 1. mechanism and pathways of allergic inflammation of the nasal mucosa

members lead to infiltration of neutrophils and Th1-bias inflammation, which differs from IL-25 as a result of the C-terminal and N-terminal structure polymorphism and the number of cysteine residues.

Further cloning experiments of the full-length IL-25 sequence from both mouse and human have revealed that the IL-25 open reading frames (ORF) encode for 169 and 161 amino acid residues in mouse and human, respectively. The amino acid sequences then formed the mature IL-25 proteins weighing 17.5 kDa in mouse and 16.7 kDa in human, respectively. Further analysis of the protein translated from the ORF showed important homologies between IL-25 derived from mouse and human, including the same N-terminal leader sequence and a single potential N-linked glycosylation site [5••]. These results provided the theoretical foundation for the investigation of IL-25 in murine models, which provide mechanistic findings relevant to the human model.

Sources of IL-25 expressing tissues and its role in allergic inflammation

While early discovery of IL-25 was in Th2 cells [1], later studies reported that IL-25 is produced in extensive sources including alveolar macrophages, bone marrow-derived mast cells, activated eosinophils and basophils, and damaged or activated nasal/airway epithelial cells [6–10]. Moreover, It is also found in multiple mucosal tissues including uterus, stomach, small intestine, kidney,

and lungs [6–10]. Following which, the rare epithelial cells with the capacity of IL-25 production, tuft cells, were subsequently found in the mouse gut. Moreover, Kohanski et al. further demonstrated the presence of another rare epithelial cell type, the solitary chemosensory cell (SCC) in healthy sinus cavity, and turbinate tissues of the human upper airway. The SCC is characterized via its expression of the taste-associated G protein gustducin and the intestinal tuft cell marker doublecortin-like kinase 1. Further, SCCs are found to occur increasingly in clusters in the sinonasal epithelia of patients with CRSwNP and serve as the predominant source of IL-25 [11].

While a myriad of cell types are found to produce IL-25, the trigger for IL-25 production may differ in different tissues. For example, bone marrow-derived mast cells produced IL-25 when stimulated with anti-dinitrophenol (DNP) IgE and DNP–human serum albumin (HSA). Its production causes IgE binding leading to mast cells crosslinking, where the levels of the IL-25 mRNA were found to be comparable with those produced by polarized Th2 cells [12]. Alveolar macrophages were also reported to potently secrete IL-25 with the treatment of TiO₂ particles in vivo and in vitro through immunostaining methods [13]. Substantial levels of IL-25 transcripts were also reportedly found in both resting and activated peripheral blood eosinophils and basophils from healthy or allergic subjects, measured by quantitative real-time PCR (qPCR) [8]. IL-13 treatment to the in vitro air-liquid interface (ALI) polyp cultures also significantly increased the apical secretion of IL-25 localized in the SCCs mentioned above [11]. Based on several experimental observations, Kouzaki et al. further verified that IL-25 is preformed and stored or sequestered in the cytoplasm of airway epithelial cells. Upon exposure to common allergens containing protease activities such as house dust mite (HDM), epithelial-derived IL-25 was rapidly released which then lead to the induction of allergic inflammation [14]. Due to its pre-formation, this feature allows it to mediate innate immunity, responding rapidly against incoming allergen. As a result, increased IL-25 mRNA level and an enriched number of IL-25-positive-epithelial cells were often detected in the human nasal mucosa of patients with HDM-sensitized AR. Congruent with this finding, the administration of endogenous cysteine and serine protease inhibitors significantly inhibited the secretion of IL-25 [15, 16]. All of these studies showed that IL-25 is produced from rather extensive sources, including but not limited to innate immune cells, adaptive immune cells, and structural cells from nonhematopoietic lineage.

IL-25 receptors distribution and function (IL25R/IL17RB)

IL-25 receptor (IL-25R), also known as EVI27, or IL17 receptor homolog 1 (IL-17Rh1), is a heterodimer composed of IL-17RA, a common subunit for IL-17A, IL-25 and IL-17F, and IL-17RB, a 502 amino acid single transmembrane protein with higher affinity to IL-25 than IL-17B [17]. In stark contrast with IL-25 which is extensively expressed in multiple cell types, IL-25R are more restricted in their expression [7]. It was reported that TSLP-DC (dendritic cells activated by thymic stromal lymphopoietin)-activated memory Th2 cells is by far the cell type found to express sustained IL-25R. In addition, while both resting and activated memory Th2 cells have IL-25R transcripts detected in them, only activated memory Th2 cells expressed detectable surface IL-25R [8]. Angkasekwina and

colleague further reported that IL-17RB expressed in naive T cells was downregulated during Th1 and Th17 differentiation, while it was found to be upregulated in Th2 differentiation in an in vitro setting of naïve CD4⁺ T cells. The finding hence suggests that IL-25R was restricted in their expression and is largely confined to Th2 cells [18]. Surprisingly, IL-9 producing Th9 cells, an inhibitor of Th2 differentiation is also found with enhanced IL-17RB expression when treated with IL-4 and tumor growth factor β (TGF- β). The finding suggested that Th9 cells also respond to IL-25 and the dual IL-17RB expression of Th9 and Th2 cells potentially serve as a feedback loop against overproduction of Th2 cells and their associated factors in response to IL-25 [19].

Other than Th2 and Th9 cells, further investigation also identified invariant NKT, APC, and airway smooth muscle cells that expressed IL-17RB under specific conditions [17]. Using gene expression microarrays, Wang et al. reported for the first time that IL-17RB was expressed on human basophils from patients with seasonal allergic rhinitis (SAR). They further showed that the activation of IL-17RB by IL-25 inhibited basophil apoptosis and augmented IgE mediated basophil degranulation, releasing inflammatory mediators including histamine, LTC₄, IL-4, and IL-13 [20]. Nonetheless, the activation of IL-17RB on basophils did not contribute to the upregulation of cytokine release and adhesion molecule expression, which were different from its effect on eosinophils [20]. On top of that, Matsumoto et al. have also detected significant upregulated IL-17RB gene transcripts in basophils of patients with SAR via gene expression microarrays [21]. By using double sequential immunohistochemistry assay, MBP⁺(major basic protein)eosinophils were found to be among the principal cells expressing IL-17RB to exert its immunoreactivity in the experiment of Corrigan et al. [22]. As the field of IL-25 and IL-25 responsive cells grows, novel populations of innate cells such as the Lin⁻ckit⁺Sca1⁺IL-17RB⁺non-B/non-T (NBNT) cells capable of producing type 2 cytokines and a novel granulocytic population, termed type 2 myeloid cells (T2M), were all found to express IL-17RB [17]. Meanwhile, many studies suggested that group 2 innate lymphoid cells (ILC2), a new lymphoid subset that produced type 2 cytokines IL-5 and IL-13, also expressed IL-17RB/IL-17RA on the cell surface to respond to IL-25 secretion [23••]. This discovery suggested that IL-25-mediated allergic inflammation may be exerted via both T-dependent and T-independent pathways through innate and adaptive cells expressing IL-25R.

Biophysiological activities of IL-25 in acquired immune responses

It has been established that response to IL-25 expression by activated Th2 cells will lead to the production of IL-4, IL-5, and IL-13 by major histocompatibility complex (MHC) class II-expressing accessory cells in the airway mucosa [5]. IL-4 will in turn induce the differentiation and polarization of Th0 cells to Th2 bias which further promotes the proliferation of B cells towards IgE isotype switch. IL-5 further contributes to the allergic inflammation via the sustained recruitment and activation of eosinophils via a positive feedback of eotaxin production. Finally, IL-13 increases the mucus production by hyperplastic goblet cells, causing extensive mucus secretion. Following the discovery of their

biophysiological activity, a number of studies with murine models further verified that exogenous administration and overexpression of IL-25 augment Th2 cell-mediated inflammation. In contrast, neutralizing/blocking of IL-25 or IL-25-deficient mice showed significantly reduced Th2 cytokine production and eosinophil infiltration [24•, 25•, 26•, 27•, 28, 29•, 30•, 31•].

Angkasekwinai et al. went on to verify that IL-25 evoked Th2 cell differentiation by potentiating early IL-4 production as well as reinforcing the effector Th2 cells' expansion and cytokine production [18]. Xu et al. also detected a significant increase of IL-25, together with TSLP, an initiator of allergic cascade and IL-17A, a potent neutrophil chemotactic factor that also inhibits eosinophil infiltration upon nasal administration of dsRNA, a viral mimic. The finding suggested that IL-17A and IL-25 played antagonistic roles during nasal inflammations and that IL-25 was possibly dominant over IL-17A in promoting allergic mucosal inflammation [32, 33]. Congruently, IL-25 were also showed to ameliorate Th1/Th17 responses by attenuating Th1 transcription factor mRNAs such as T-bet and STAT4 as well as downregulating the secretion of proinflammatory cytokines TNF- α , IFN- γ , and IL-17A of Th17 cells in inflammatory bowel disease [33]. In addition, naïve CD4⁺T cells treated with anti-CD3 and anti-CD28 in the absence of IL-25 predominantly differentiated into Th1 cells, producing INF- γ and TNF- α . When IL-25 was administered, naïve CD4⁺T cells in turn differentiated into IL-4, IL-5, and IL-13 producing Th2 cells, also downregulating Th1 cells in the process [18]. Moreover, the IL-25 mRNA level in human nasal epithelial cells showed a positive correlation with Th2 markers such as ECP and GATA3 [16]. Furthermore, IL-25-neutralizing antibody treatment was also found to lead to significant reduction of nasal polyp size, attenuation of mucosal edema and inflammatory cell infiltration, and reduction of CCL11/CXCL2/ICAM-1 (intercellular cell adhesion molecule-1) expression in the airway epithelia [34••]. Therefore, IL-25 plays critical roles in the promotion of Th2-skewed acquired immune responses.

Biophysiological activities of IL-25 in innate immune responses

The recent discovery of innate lymphoid cells has furthered the understanding of innate immune involvement in allergic mucosal inflammation. ILCs exhibited similar morphological characteristics to that of lymphocytes, but express neither T/B cell antigen receptors (TCR or BCR) nor lineage (Lin) markers associating with other immunocyte lineages. ILCs are categorized into three groups based on their cytokine production. Among them, ILC2s are capable of producing IL-5, IL-9, and IL-13 in response to IL-25 and IL-33 and were initially labeled as Lin⁻ckit⁺Sca1⁺IL-17RB⁺ non-B/non-T (NBNT) cells which included natural helper cells, nuocytes, and ILC2s innate helper 2 cells. It was found that intra-nasal administration of IL-25 to mice deficient in T cells and B cells resulted in an allergic response characterized by augmented IL-5 and IL-13 production, which implicated ILC2s role in the response. Furthermore, IL-17RB and IL-17RA were also detected to be expressed in ILC2s [23]. Further experiments then verified that IL-25-activated ILC2s indeed contributed to IL-5 and IL-13 upregulation by using transferring IL-25-activated ILC2s into RAG-deficient mice which lacked both T and B cells but retained ILC2s [35]. In human airway context, strong ILC2 effects in response to IL-25 were observed

in the nasal polyps of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) [36]. Collectively, IL-25 thus functions as a master regulator that mediates both innate and adaptive via combined activation of ILC2s and Th2 cells to evoke sustained allergic mucosal inflammation. The summary of the roles of IL-25 in promoting type 2 inflammation is shown in Fig. 2.

IL-25R-dependent IL-25 signaling pathways

With IL-25's involvement in multiple Th2 activation pathways, its signaling pathway is therefore in need of further elucidation to provide the basis of targeting IL-25 pathways in the future. In 2005, it was reported that IL-25

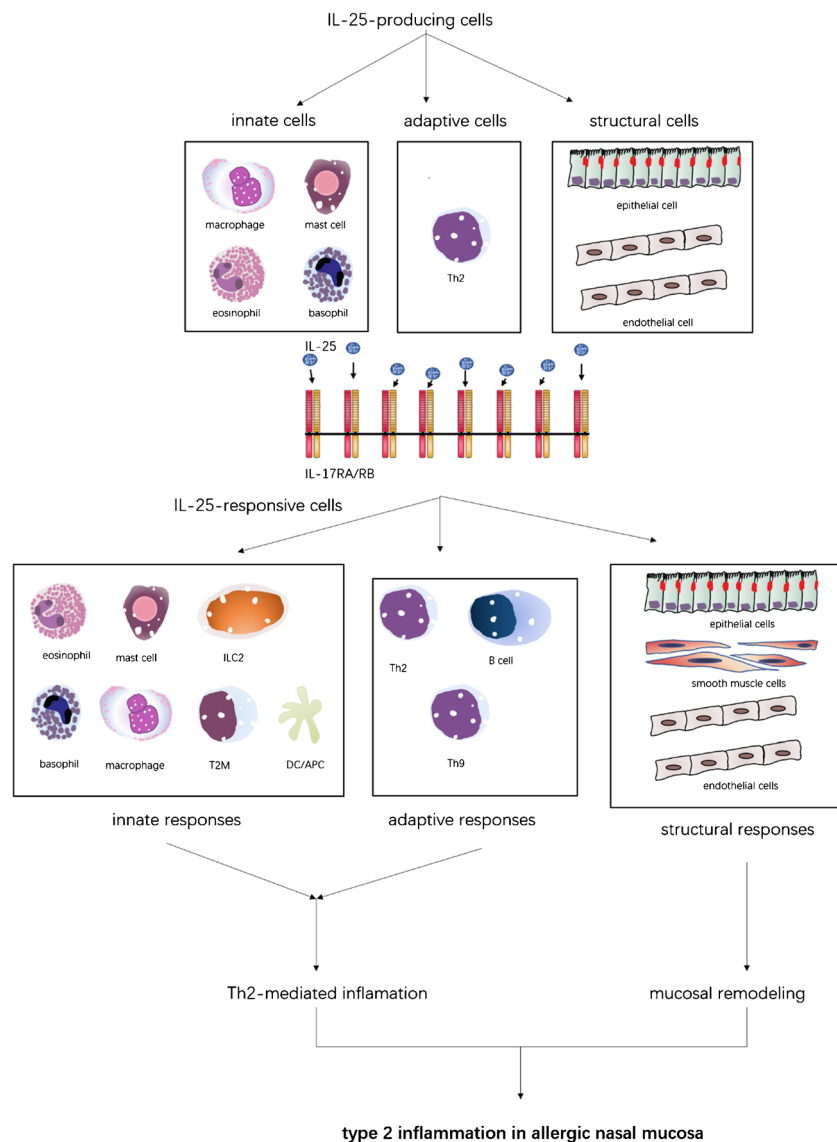


Fig. 2. IL-25's role in promoting type 2 inflammation in allergic nasal mucosa

activated the common intracellular transcriptional factors p38 mitogen-activated protein kinase (p38 MAPK), nuclear factor(NF)- κ B, c-Jun amino-terminal kinase (JNK) via phosphorylation. The phosphorylation then allows the gene transcription of chemokines including monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1, IL-6, and IL-8, which lead to recruitment of inflammatory cells in the ensuing inflammation [31]. These inflammatory and chemotactic factors are largely responsible for local tissue damage resulting in the exacerbation of local allergic inflammatory responses. Soon after, another experiment on Th2 cells demonstrated that IL-25 together with CD3 and CD28 co-stimulated Th2 cells to proliferate, producing cytokine/chemokine via the intracellular JNK, P38 MAPK, and NF- κ B pathways, while IL-25 alone was insufficient to evoke these bioactivities [31]. Upon co-stimulation, the phosphorylation of JNK, P38, MAPK, and NF- κ B leads to the upregulation of IL-25R on Th2 cells, followed by the increased secretion of IL-4, IL-5, IL-6, IL-13 as well as CXCL10, CXCL9, and CCL5. Correspondingly, the treatment of I κ B- α phosphorylation inhibitor, JNK inhibitor, and p38 MAPK inhibitor significantly suppressed not only the viability of Th2 cells but also their ability to produce Th2 type cytokines [37].

According to the studies of the sources of IL-25 and IL-25R above, it is interesting to note that activated Th2 cells were among the sources of IL-25, where IL-25-induced upregulation of IL-25R resulted in the further increase of Th2-derived IL-25. This meant that IL-25 acted via autocrine secretion forming a positive feedback loop to continuously promote Th2 cytokine production, perpetuating type 2 allergic inflammation. Systemically, by using a murine model for allergic rhinitis, it was found that there are positive correlations between both p38 mitogen-activated protein kinase (p38MAPK) and NF- κ B with IL-25. The finding validated previous IL-25/IL-25R interactions where an allergen challenge signals via IL-25 the combined p38MAPK and NF- κ B pathways to up-regulate the downstream cytokine and chemokine production [38, 39]. Additionally, it is reported that NF- κ B activation may also contribute to the

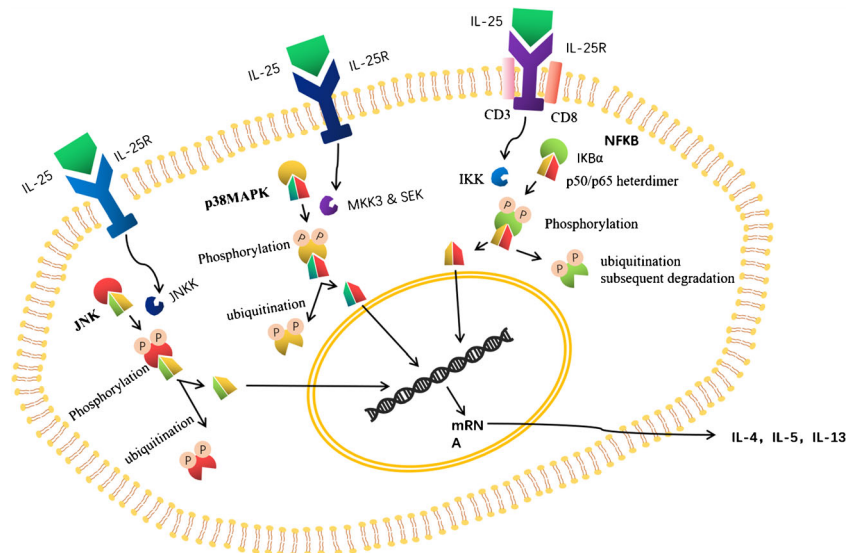


Fig. 3. IL-25R-dependent IL-25 signaling pathways

sustained expression of IL-25. NF- κ B is usually sequestered in the cytoplasm by binding the members of the inhibitor κ B (I κ B) family of inhibitor proteins [40]. Phosphorylation of I κ B followed by its ubiquitination and its subsequent degradation resulted in the activation of NF- κ B, which purportedly sustains IL-25 expression.

Furthermore, it is also reported that epithelial-derived adaptor protein NF- κ B activator 1 (ACT1, also known as CIKS—connection to I κ B kinase (IKK), SAPK stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK), contains a conserved sequence segment called SEFIR (similar expression to fibroblast growth factor genes) domain. The domain was found to play a pivotal role in IL-25 mediated pathway, because it was recruited to IL-25R which also contains the conserved SEFIR in its cytoplasmic domain and the dimerization of the SEFIR domains in both ACT1 and IL-25R initiated the subsequent signal transduction [41, 42]. Hence, ACT1 is also a promising therapeutic target to ameliorate nasal mucosal allergic inflammation mediated by IL-25 through this reported interaction. The complete pathway known so far on IL-25 signaling is summarized in Fig. 3.

IL-25 promoted type 2 allergic responses and its relationship with other inflammatory sinonasal mucosal inflammatory conditions

Allergic inflammation has long been referred to associate significantly with other sinonasal mucosal inflammatory conditions such as CRS [43]. There has been a number of investigations that analyzed the NPs of patients with CRSwNP collected from functional endoscopic sinus surgery (FESS). The investigations showed that the NPs contained large proportions of ILC2s, Th2 cells, and IL-25 when compared to the uncinate process (UP) of patients with CRSsNP and healthy controls and that IL5 and IL13 transcripts were more abundant in CRSwNP patients synchronously [35, 44, 45]. In Asian patients, IL-25 was upregulated in both CRSsNP and CRSwNP, where higher levels is observed in CRSwNP, indicating that IL-25 was involved in CRS inflammation among other inflammatory regulators [34].

In the context of CRSwNP, patients with eosinophilic chronic rhinosinusitis (ECRS) showed significantly higher population of IL-25 and IL-17RB expressing tissue memory CD4⁺ T cells than those with non-eosinophilic CRS (NECRS), a difference which resulted in eosinophilia and augmentation of IL-5 and IL-13 production [46–48]. Using another approach, Chen and Hong categorized patients with CRSwNP into asthma, asymptomatic airway hyperresponsiveness (AAHR), and non-AHR (NAHR) subgroups to reveal significantly increased NP tissue IL-25 levels in patients with CRSwNP. The increased NP tissue IL-25 levels thus served as a risk factor to predict concomitant AHR and asthma in CRSwNP with 93.5% sensitivity and the 60.0% specificity using a tissue IL-25 protein cutoff level of 5.0 pg/mL [49•]. Furthermore, Miljkovic et al. observed increased ILC2s in NPs of CRSwNP patients congruent with previous reports, though with decreasing IL-25 mRNA levels being conflicting to similar research [35]. These different results could be attributed to various sampling and the sinonasal microbiome of the individuals. In a study with the same sample size as

Miljković's, Hong et al. noted a stratification of IL-25 expression in CRSwNP patients, namely, IL-25^{high} and IL-25^{low}, where IL-25^{high} subgroup demonstrated greater CT scores and endoscopy scores than those in IL-25^{low} subgroup [50••]. The utility of IL-25 in other inflammatory diseases still remains a point of contention, as Ozturan et al. reported that neither serum IL-25 nor tissue IL-25 showed any statistically significant difference among groups in a study composed 20 CRSwNP, 20 CRSsNP, and 20 control group patients [51]. Hence, further studies that delve into the role of IL-25 beyond allergic mucosal are required to ascertain its role in chronic-allergic-infectious inflammation of nasal mucosa.

Nevertheless, as it stands most of the related studies elucidated the increased expression of IL-25 was associated with Th2-biased inflammation and tissues eosinophilia in CRSwNP patients by activation of Th2 cells and ILC2s. Thus, IL-25 may be a promising therapeutic target and an indicator for the management of eosinophilic CRSwNP patients, on top of its utility in the allergic inflammatory mucosa.

Conclusions

In conclusion, a further understanding of the pathogenesis of allergic nasal mucosal inflammation has revealed insights pertaining to IL-25 and its effects as a master regulator of type 2 inflammation from the epithelium. This review collated results that showed IL-25 serve as a bridge between the epithelial cells and inflammatory cells in the sinonasal mucosa in promoting type2 allergic inflammation. Additionally, IL-25 links the innate immunity and acquired immunity via the feedback between ILC2s and Th2 cells under the complex signaling pathways involving various type 2 signaling factors such as p38 MAPK, NF-κB, and JUK, thus serving to amplify and perpetuate allergic inflammation. IL-25 also provided the link between specific cases of other sinonasal inflammatory conditions such as CRSwNP with allergic inflammation where its expression typically resulted in more severe mixed inflammatory conditions. Therefore, IL-25's role in local inflammation of the airway is extensive and may present a viable target for future biologics development.

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Compliance with Ethics Guidelines

Conflict of Interest

Shumin Liao, Kai Sen Tan, Mingmin, Wei Liao, Yuan Chen, and Haiyu Hong declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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