The Role of New IL-1 Family Members (IL-36 and IL-38) in Atopic Dermatitis, Allergic Asthma, and Allergic Rhinitis

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Abstract
Purpose of Review Since the discovery of its very first member in 1974, the IL-1 family has expanded into a group of 11 potent molecules which are essential in both innate and acquired immunity. Pro-inflammatory cytokines IL-36α, IL-36β, and IL-36γ and their receptor antagonists IL-36Ra and IL-38, which belong to the IL-36 subfamily, are some of the most recently identified members. Recent studies show that these members possess pro-inflammatory and anti-inflammatory activities and may take part in the pathogenesis of allergy. In this review, the involvement and importance of these newly described IL-1 family members in the most common allergic diseases, i.e., atopic dermatitis (AD), allergic asthma, and allergic rhinitis, will be discussed.

Recent Findings Dysregulation of IL-36 and IL-38 was observed in the skin and respiratory tract of AD, allergic rhinitis, and allergic asthma individuals. Although the upregulation in IL-36α and IL-36γ observed in the lesional skin of AD patients was unexpectedly small, IL-36 may play an important role in AD pathogenesis especially upon Staphylococcus aureus colonization. While IL-36γ regulates eosinophils to induce an inflammatory response in allergic rhinitis, IL-36α was found to regulate Th17 immunity. IL-36 receptor antagonists, IL-36Ra and IL-38, however, both show promising anti-inflammatory activities against allergic asthma. Of note, IL-38 in allergic asthmatic children is significantly lower than their healthy counterparts, while the anti-inflammatory effects of IL-38 in allergic asthma exacerbation upon viral-like infection were demonstrated in in vitro, HDM-induced, and humanized mice models.

Summary Dysregulated expression of IL-36 and IL-38 observed in allergic patients and mice models revealed that they may have essential roles in the pathogenesis in AD, allergic rhinitis, and allergic asthma, especially during the host defense against pathogens at inflammatory sites. Their receptor antagonists, IL-36Ra and IL-38, could also be promising biologies in the control of allergy. Since allergic diseases are phenotypically complex, contradictory data obtained in different studies may be explained if further stratification of disease endotypes is explored. Genetically modified mice model and investigation in anti-IL-36 treatment may be useful to characterize the therapeutic potential of these cytokines in the regulation of allergy in the future.

Keywords Allergic asthma · Atopic dermatitis · IL-36 · IL-38

Introduction
Allergy is a hypersensitivity reaction triggered upon the exposure of allergens. It is a complex immunological disorder that is influenced by genetics and the environment. The inflammatory response involved is often Immunoglobulin E (IgE) mediated and can therefore be diagnosed based on the measurement of IgE antibodies in serum or positive reaction in skin prick tests, together with the clinical and family history of the patients. The prevalence of allergy has been increasing, especially in high-income countries. According to the European Academy of Allergy and Clinical Immunology, it is estimated that more than half of all Europeans will develop allergy [1]. The alarming increase in allergic patients poses both economic and societal burdens.
The atopic march describes the typical disease progression of atopic patients—beginning with atopic dermatitis (AD) during infancy, followed by allergic asthma, and lastly, developing into allergic rhinitis in later childhood. AD is one of the most common allergic skin disorders, which affects up to 20% of children and 10% adults worldwide [2]. It is clinically characterized by eczematous lesions, and histologically characterized by edema between epidermal keratinocytes, thickening of the epidermis, and infiltration of inflammatory cells such as eosinophils. T helper (Th) 2–predominant immune response is in large part the cause of acute AD inflammation. Th1-like immune response, on the other hand, is observed in chronic AD [3]. Recent findings show that an imbalance of skin microbiota, such as the enrichment of *Staphylococcus aureus* (*S. aureus*) in lesional skin, also contributes to the dysregulation in the immune system and disruption of the skin barrier [4]. Infiltration of Th17 cells can induce interleukin (IL)-17, IL-17F, and IL-22 production and clear pathogens by the recruitment of neutrophils. Although IL-17 can increase antimicrobial peptides (AMPs), which are important in the innate immune response, IL-22 expression is the predominant Th17 cytokine found in AD [5].

Allergic asthma is an allergic inflammatory disease of the lower airway. Asthma affects around 300 million people worldwide [6]. Although it has heterogenous phenotypes, it is generally characterized by reversible airflow obstruction, airway hyper-responsiveness, and episodic respiratory symptoms such as wheezing, shortness of breath, and chest tightness. Histologically, eosinophil infiltration into the lung tissue, mucus over-secretion, and airway remodeling are often observed. Viral infection is one of the risk factors of asthma and its exacerbation. The first wheezing illness for most asthmatic children originated from viral infection [7]. Allergic rhinitis, on the other hand, is the IgE-mediated inflammatory disease of the upper airway induced upon allergen exposure at the nasal mucosa [8]. Allergic rhinitis affects 50% of the population in some countries [9]. Clinical symptoms include sneezing, itching, and persistent nasal obstruction and mucous discharge [10]. It is also often associated with allergic conjunctival symptoms [11]. Histologically, it is characterized by the infiltration of eosinophils and mucus production. Both Th2 and Th17 cell immunities are involved in the pathogenesis of these two airway diseases [12].

**New Members in the IL-1 Family**

Members in the IL-1 family are characterized by the conserved three-amino-acid structure, with the first amino acid containing an aliphatic side chain functional group and aspartate as the last amino acid. The IL-1 family is made up of 11 members, namely the well-known pro-inflammatory cytokines IL-1α and IL-1β, their receptor antagonist IL-1Ra, the IL-1β-related cytokine IL-18, the Th2-driving cytokine IL-33, and six recently described members IL-36α, IL-36β, IL36y, IL-36 receptor antagonist (IL-36Ra), IL-37, and IL-38. IL-1 family members contribute to both innate and acquired immune responses and have been widely reported to play important pathological roles in autoimmune diseases, cancers, degenerative diseases, and infectious diseases [13••]. Within the IL-1 family, only IL-1Ra contains a signal peptide and can be readily secreted; all other members require N-terminal processing to function as agonists and antagonists. When these pro-peptides are cleaved, a mature cytokine capable of receptor binding will be generated [14]. The length of the pro-peptides of their precursors was used to further categorize these cytokines into three subfamilies, i.e., the IL-1, IL-18, and IL-36 subfamilies [14]. Among the three subfamilies, members of the IL-36 subfamily (i.e., IL-36α, IL-36β, IL-36γ, IL-36Ra, and IL-38) possess the smallest pro-peptide, followed by those in the IL-18 subfamily (i.e., IL-18, IL-37). Recent studies revealed that IL-18 and IL-36 subfamily members also take part in the immune regulation in allergy. Targeting the inflammation pathway is a promising remedy for treating allergic disorders.

There are various splice forms of IL-37, namely IL-37a, IL-37b, IL-37c, IL-37d, and IL-37e, which are detectable in different human tissues [15]. Among them, isoform IL-37b, which is expressed in PBMC, lymph nodes, and lungs, has the largest molecular weight with the most complex biological functions [15, 16]. In the past decade, although studies regarding the function of IL-37 on AD are scarce, the pathological roles of IL-37 and its molecular mechanisms involved in allergic asthma [17–25] and allergic rhinitis [26–28] have been widely explored. Of note, bacterial TLR2-activated eosinophils, the major effector cells of both allergic asthma and AD, can be regulated by IL-37 isoform IL-37b upon bronchus infection via interacting with human bronchial epithelial cells in allergic asthma models [25]. This provides a new direction to the potential therapeutic application of IL-37 in AD. Since several comprehensive reviews have already summarized the anti-inflammatory potential of IL-37 in treating allergic diseases [29–35], the current review will not cover experimental work related to IL-37 and allergy.

**Role of IL-36 Subfamily Members in the Regulation of Atopic Diseases**

The IL-36 subfamily consists of three agonists: IL-36α (or IL-1 family member 6 (IL-1F6)), IL-36β (or IL-1F8), and IL-36γ (or IL-1F9), as well as two antagonists: IL-36Ra (or IL-1F5) and IL-38 (or IL-1F10). IL-36 cytokines were first identified by in silico studies from 2000 to 2002. The three IL-36 cytokines IL-36α, IL-36β, and IL-36γ are proteins synthesized by distinct sequence with a conserved A-X-Asp IL-1 family...
amino acid motif, where A is an aliphatic amino acid [36]. Specific N-terminal truncation by various enzymes is required for the generation of active forms of these IL-36 agonists because the sequence homology around their cleavage sites is not similar [36–38]. IL-36α, IL-36β, and IL-36γ act as agonists and bind to the heterodimeric receptor complex of IL-36 receptor (IL-36R) and IL-1 receptor accessory protein IL-1RAcP1 and trigger downstream signaling cascade including MyD88 adapter protein complex, NF-kB, and MAPK pathways to promote inflammation [38]. On the other hand, IL-36Ra and IL-38 act as antagonists and bind to IL-36R, blocking intracellular signaling, and thus exerting anti-inflammatory activities [39••]. Although IL-36 subfamily members have been widely reported to contribute to the pathogenesis of AD, allergic rhinitis, and allergic asthma, reviews on the accumulated experimental data are limited. The current review, therefore, sought to summarize the recent findings of the pathological roles and potential use of the members IL-36α, IL-36β, IL-36γ, IL-36Ra, and IL-38, particularly in allergic diseases.

**IL-36 and Atopic Dermatitis**

IL-36α, IL-36β, and IL-36γ are differentially expressed not only in different layers of the epidermis, but also in different skin areas of the patient [40]. The involvement of IL-36 subfamily members in various kinds of inflammatory skin diseases, especially allergic contact dermatitis (ACD) and psoriasis, has been widely reported in the last decade. In vivo studies show that IL-36α, IL-36β, and IL-36γ are differentially expressed in epidermal layers of the skin of ACD patients [40], with an over-expression in the skin areas with positive patch test results. Although the expression of IL-36Ra in the lesional skin of ACD patients is comparable to that observed in healthy subjects, injection of recombinant IL-36Ra to the non-involved skin of patients reduced the expression of pro-inflammatory cytokines IL-36α, IL-36β, and IL-36γ. This indicates that IL-36Ra could be a potential therapy for treating skin disease such as ACD, and potentially for AD as well, as AD is a skin disorder with similar clinical phenotypes as ACD.

When compared with that in the non-involved skin, significant upregulation of IL-36α and IL-36γ is found in the psoriatic skin of psoriasis patients, but, surprisingly, not in the eczematous skin of atopic dermatitis patients (Table 1) [41]. In line with other studies, Th2 cytokines were found to be upregulated in the skin of AD patients [41]. RNA sequencing and RT-PCR also revealed that IL-36α and IL-36γ mRNA expressions in lesional skin of moderate-to-severe AD patients were increased when compared with those in non-lesional skin, but the dysregulation was not as significant as the psoriasis patients [42]. Although these results indicate that IL-36 cytokine may play a limited role in AD, the significant difference in IL-36 expression between lesional and non-lesional skin suggested that IL-36 cytokines are potential markers to help for the assessment of the improvement in skin lesion in clinical trials.

*S. aureus* is an AD-associated gram-positive bacterium that can be found in 70% of the lesional skin of AD patients [47–51], suggesting that *S. aureus*–driven immune responses may contribute to AD pathology. Various IL-1 family members IL-1α, IL-1β, IL-18, and IL-33 contribute to the host defense against *S. aureus*, and previous studies have shown that IL-36 plays a role in skin inflammation upon *S. aureus* exposure [52, 53]. *S. aureus* colonization triggered IL-36α expression in the epidermis and induced pro-inflammatory IL-17A production by T cells via the IL-36R/MyD88 pathway [52]. Production of IL-36-mediated T cell responses was observed at the epidermal layer, but not in the intradermal layer, implying that the immune response depends largely on the predominant cells that the *S.aureus* is exposed to in the skin. Virulence peptide phenol-soluble modulins (PSMs) expressed by *S. aureus* were reported to be responsible for damaging keratinocytes in the epidermis, inducing their release of IL-1α and IL-36, and hence orchestrating cutaneous inflammation [53]. IL-36 cytokines could also regulate regnase-1 (Reg1), an immunomodulator of skin inflammation, in keratinocytes in a mouse model of contact hypersensitivity [54]. Moreover, IL-36γ is involved in the progression of acute AD to chronic AD [55]. Although there is currently no study showing the efficacy of the use of anti-IL-36 in treating AD, the above studies suggest that targeting the IL-36 inflammatory axis has therapeutic potential in controlling AD.

**IL-36 and Allergic Rhinitis**

Similar to the skin, IL-36 cytokines distribute differentially in the nasal cavity, with IL-36α and IL-36β production localized to the inflammatory cells in lamina propria, and IL-36γ production localized to nasal epithelial cells and neutrophils in nasal polyps [56]. IL-36γ in nasal epithelial cells can be upregulated by IL-17, IL-25, and IL-33 [43], while IL-36γ of normal bronchial epithelial cells can also be increased upon double-stranded RNA, IL-1β, TNF-α, and IL-17 stimulation [57, 58]. The distinct response towards different stimuli may be due to the differential IL-36R expression in the nasal cavity. In nasal polyps, the receptor for IL-36 cytokines, IL-36R, is prominently expressed on neutrophils; however, mononuclear cells such as CD3+CD8+ and CD3+CD8− T cells do not express IL-36R [56]. Strikingly, IL-36R expression on eosinophils purified from the peripheral blood of allergic rhinitis patients and the neutrophils purified from the healthy individuals could be significantly upregulated by allergen house dust mite (HDM) *Dermatophagoides pteronyssinus* group 1 (Der p1) [43, 56].
Table 1  New members in the IL-36 subfamily, their receptors, and mRNA or cytokine dysregulation in allergic patients

| Subfamily | Member | Receptors | Co-receptors | mRNA expression/cytokine level in allergic patients |
|-----------|--------|-----------|--------------|---------------------------------------------------|
| IL-36     | IL-36α | IL-1R6 (or IL-36R) | IL-1R3 | ↑† |
|           | IL-36β |           |              | ↑* |
|           | IL-36γ |           |              | ↑* |
|           | IL-36Ra|           |              | ↓* |
|           | IL-38  | IL-1R9    | (or TIGIRR2)| ↑> |

† mRNA expression level of the lesional skin region when compared with that of the non-lesional region of AD patients [41, 42]
* mRNA expression and cytokine levels in serum of patients when compared with that of healthy individuals [43, 44]
# mRNA expression level on PBMC and SMNC as well as cytokine levels in serum and induced sputum when compared with that of healthy individuals [45]
> Serum level in patients with or without steroid treatment when compared with that in healthy individuals [46]
n.s., statistically insignificant

Although studies investigating the role of IL-36 cytokines in allergic rhinitis are scarce, allergic rhinitis patients have significantly higher serum IL-36α, IL-36β, IL-36γ, IL-36Ra, and IL-36R mRNA expression of eosinophils than healthy individuals [43, 44]. Among the IL-36 cytokines, IL-36γ is the highest [43]. Contrary to patients with chronic rhinosinusitis, the increase in IL-36γ expression in allergic rhinitis patients is positively correlated to the number of eosinophils, but not neutrophils [43, 56]. IL-36γ expression is also positively correlated to the concentration of serum eosinophil cationic proteins. On the other hand, IL-36γ can regulate eosinophil function by promoting their survival, activation, and migration via intracellular p38 mitogen-activated protein kinase (MAPK) and mitogen-activated protein kinase kinase (MEK) pathways [43]. These results provide evidence that IL-36γ may be an important pathway to control inflammation in allergic rhinitis via regulation of its principal effector cells, eosinophils, in allergic inflammation.

IL-36α is another potential target for controlling inflammation in allergic rhinitis, because it exhibits a direct effect on Th17 differentiation in allergic rhinitis via phosphoinositide 3-kinase (PI3K)/AKT and extracellular signal-regulated kinase (ERK) pathways [44]. Serum IL-36α concentration in allergic rhinitis patients was found to be exclusively correlated with serum IL-17 and IL-23 levels, suggesting a role of IL-36α in Th17 regulation. Moreover, a mouse model of allergic rhinitis revealed that anti-IL-36α suppressed ovalbumin (OVA)-specific IgE, nasal rubbing, sneezing, and Th17 cells in OVA-induced mice. Similarly, blocking IL-17 and IL-23 alleviated nasal symptoms and Th2 inflammation as well as IgE production [44]. Th17 differentiation of peripheral blood mononuclear cells (PBMC) could also be promoted by IL-36α [44]. However, the role of IL-36R in Th17 response upon IL-36α stimulation is yet to be elucidated.

IL-36 and Allergic Asthma

Several studies have indicated that allergic rhinitis is a common comorbidity of allergic asthma and is associated with increased asthma severity [59]. Similar to patients with allergic rhinitis, patients with both allergic rhinitis and allergic asthma express significantly more serum concentration and mRNA expression level of IL-36α, IL-36β, IL-36γ, IL-36Ra, and IL-38, when compared with their healthy counterparts [43]. Interestingly, upon treatment with inhaled glucocorticoids, pediatric patients with allergic asthma were found to have significantly lower IL-36Ra expression in PBMCs and sputum mononuclear cells (SMNC) and a lower serum and sputum-induced IL-36Ra levels than the healthy children [45]. Recombinant IL-36Ra protein could not only inhibit the release of pro-inflammatory cytokine IL-1β, TNF-α, IL-6, and IL-17 from LPS-stimulated PBMC and SMNC ex vivo, but also suppressed airway hyper-responsiveness and inflammatory cell infiltration to the lung in OVA-induced asthmatic mouse model [45]. Signaling studies further confirmed that IL-36Ra exerts its anti-inflammatory activity mainly through the inhibition of the IL-36R/NF-κB pathway. Being the antagonist of IL-36 that targets the pro-inflammatory receptor IL-36R, IL-36Ra possesses anti-inflammatory activities in allergic asthma [45].

IL-38 and Atopic Dermatitis

IL-38 was first identified by a high-throughput cDNA screening approach in 2001 [60, 61]. Due to its high genomic, amino acid consensus sequences, and protein structure homologies shared with other IL-1 members, as well as its ability to bind to soluble IL-1 receptor type I (IL-1RI) and IL-36R, it was characterized as a member of the IL-1 family [39, 60, 61].
IL-38 gene has close proximity to the IL-1Ra and IL-36Ra genes and shares 41% homology with IL-1Ra and 43% homology with IL-36Ra. Therefore, it is proposed as an antagonist of IL-36R signaling [61, 62]. Polymorphisms of IL-38 are associated with increased susceptibility of various chronic auto-inflammatory diseases [63–66]; however, the polymorphism associated with allergies was unclear. IL-38 protein is expressed in the spleen, thymus, fetal liver, basal epithelium of the skin, and proliferating B cells in the tonsil; lowly expressed in the heart and placenta; but not expressed in T cells or monocytes in the tonsil [60].

Although IL-38 has been postulated as an antagonist of the IL-36 receptors, the anti-inflammatory properties of IL-38 in skin inflammation remain unclear. Similar to IL-36 cytokines, IL-38 is differentially expressed in the skin. In humans, basal epithelia of the skin are reported to be the main source of IL-38 [60], while in mouse, IL-38 expression is found in keratinocytes, but not in dermal fibroblasts [67]. IL-38 is predominantly and exclusively localized in the cytoplasm of the keratinocytes, where it can interact with dextrin/actin-depolymerizing factor (DSTN) [68]. The function of such an interaction in AD remains to be elucidated. A research group has recently suggested that activated mast cells could possibly trigger IL-38 production to block IL-36 function in allergic skin [69]. However, IL-38 was controversially proven to be unable to halt skin inflammation in the imiquimod-induced psoriasis-like mice model [67]. Due to the limited data currently available, it may be early to conclude that IL-38 possesses immunosuppressive potential in skin diseases such as AD.

**IL-38 and Allergic Asthma**

Although IL-38 was identified nearly 2 decades ago, its role in allergic disease still remains largely unknown. Our group has demonstrated that serum IL-38 level in school-aged allergic asthmatic patients with or without steroid treatment was significantly higher than that in their healthy counterparts. Moreover, IL-38 mRNA expression is positively correlated with its receptor IL-36R mRNA expression, but negatively correlated with anti-inflammatory regulatory T (Treg)-related IL-10 mRNA expression on PBMC [46]. Although IL-38 possesses anti-inflammatory activities in asthmatic patients, IL-38 was found to augment the release of pro-inflammatory cytokines from LPS-stimulated PBMCs and macrophages [39, 70]. Chu et al. [46] suggested that the release of immunosuppressive IL-38 can be triggered upon the increase of inflammatory cytokines, although the immunoregulation by IL-38 may be insufficient to counteract the cytokine storm. Therefore, elevated levels of pro-inflammatory cytokines IL-17, IL-6, IFN-γ, and IL-1β were still observed in asthmatic patients [46]. Quantitative analysis, however, showed that there was no notable difference in the IL-38 mRNA expression level in PBMC between the healthy controls and asthmatic patients [46], indicating that the IL-38 released might be a stored protein. When the levels of perioxidin, a marker of “Th2-related asthma,” are high, the increase in serum IL-38 is negatively correlated with the percentage of anti-inflammatory T cell subset, CD4+CD25highFoxp3+ Treg lymphocytes, implicating potential negative feedback mechanisms between the anti-inflammatory IL-38 and the suppressive Treg lymphocytes in the pathogenesis of asthma [46]. The immunoregulatory effects of IL-38 on Th17-related inflammatory response were reported by another group, who showed that depletion of IL-38 gene in apoptotic cells induced IL-6 production, thus triggering Th17 cell expansion with a diminished IL-10-producing T cell population [70]. Similar to IL-36Ra, low concentration of IL-38 suppresses memory Th17-related IL-17 and IL-22 production via binding to the IL-36R on PBMCs upon heat-killed *Candida albicans* stimulation. Nevertheless, IL-38 could induce IL-6 production in LPS-stimulated dendritic cells [39••]. This low-dose inhibition suggests that IL-38 is a non-classical IL-1 receptor antagonist [39••].

The anti-inflammatory potential and immunosuppressive mechanism involved in the action of IL-38 on asthma exacerbation was further elucidated by our group. Sun et al. showed that IL-38 significantly reduced the release of pro-inflammatory cytokines IL-6, IL-1β, CCL5, and Th1-related CXCL10 and inhibited the antiviral interferon-β (IFN-β) and intercellular adhesion molecule-1 (ICAM-1) expression on human eosinophil/bronchial epithelial cell co-culture upon stimulation by the viral RLR ligand poly (I:C)/LyoVec or infection-related pro-inflammatory cytokine TNF-α [71]. High-throughput mass cytometry and RNA sequencing analysis revealed IL-38 mediated suppression of intracellular signaling pathways and upregulation host defense-related gene and anti-allergic response genes. Airway hyperreactivity and Th2-related cytokine production were ameliorated in both HDM-induced Th2-prone allergic mice and humanized mice models upon the injection with IL-38 intraperitoneally. In line with the in vitro study, IL-38 suppressed eosinophil migration to the lung by reducing the production of the eosinophil chemoattractant CCL11 in the allergic asthmatic mice. IL-38 also decreased the production of Th2 cytokines and recruitment of Th2 cells and innate lymphoid type 2 cells. Although IL-38 slightly reduced Th17 cell number by decreasing TGF-β release, it increased the proportion of Treg cells in the lung, spleen, and lymph nodes, possibly via triggering IL-10 release. Generation of IL-38-knockout mice by CRISPR/Cas9 may be useful to validate the anti-inflammatory properties of IL-38 and its molecular mechanism involved in allergic asthma in the future [71, 72].
Conclusion

Cytokines IL-36 and IL-38 are the relatively new additions in the IL-1 family, which show diverse involvement in the pathogenesis of atopic dermatitis, allergic asthma, and allergic rhinitis. Their dysregulation and the differential expression in the skin and respiratory tract in allergic patients or mouse models prompt researchers to investigate their importance and exact role in allergy. Although the molecular mechanisms involved by IL-36 and IL-38 in AD, allergic asthma, and allergic rhinitis remain largely unknown, it is undoubted that they possess great therapeutic potential in controlling inflammation. The use of IL-36Ra and IL-38 in allergy continues to be the area to be explored.

Compliance with Ethical Standards

Conflict of Interest The authors 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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