Published in final edited form as:
Curr Opin Immunol. 2008 December ; 20(6): 697–702. doi:10.1016/j.coi.2008.09.004.

The IL-17 cytokine family and their role in allergic inflammation

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Abstract

Allergic diseases and asthma has long been hypothesized as the results of the dysregulation of type2 immune responses to environmental allergens. Recent progresses in characterizing the proinflammatory IL-17 cytokine family have added additional layer of complexity on the regulation of allergic inflammation. The delineation of IL-17-producing $CD4^+$ T cell subset (Th17) has led to the revision of Th1/Th2 paradigm and impacts our perspectives on the basis of chronic tissue inflammation. In addition, the distinctive expression patterns and biological activities of individual IL-17 cytokine member may play different roles in the regulation of the pathogenesis of allergic diseases. Understanding the cellular source and targeting cells of IL-17 cytokine family member will provide the basis to elucidate the cellular mechanism underlying allergic inflammation and improve our therapeutic approaches for allergy.

Introduction

Allergic disorders, such as asthma and atopy, are caused by the dysregulated immune responses. Research in the past decades has revealed that allergic diseases are often resulted from an imbalance between the type 2 and type 1 branches of the immune system, which are responsible for mediating humoral immune responses and delayed hypersensitivity reactions (DTH), respectively. Breakthrough studies by Mosmann and Coffman led to the discovery of two $CD4^+$ T cell subsets, T helper type 1 (Th1), and Th2, characterized by their distinct cytokine production profiles and effector functions. Th1 $CD4^+$ T cells produce large amount of IFN-γ and elicit DTH responses to clear intracellular pathogens, whereas Th2 $CD4^+$ T cells produce interleukin 4 (IL-4), IL-5, IL-13 to trigger allergic immune response and eradicate parasitic infection. Thus, the concept of Th1/Th2 paradigm has provided the basis to uncover the molecular and cellular mechanism of complex immune responses and led to the hygiene hypothesis, suggesting that dominant Th2 reaction results in allergy. Recent studies linking the discovery of IL-17 cytokine family and the analysis of IL-23 mediated immune pathogenesis previously attributed to the Th1 subsets have led to the delineation of a new effector $CD4^+$ T cell subset that produce cytokine IL-17 (termed Th17). Severe allergic diseases are often associated with chronic inflammation characterized by the infiltration and accumulations of $CD4^+$ T cells, neutrophils, eosinophils and mast cells. While cytokine IL-17 was shown to play an important role on the inflammatory process, the

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role of IL-17 cytokine members and the IL-17-producing cells during allergic inflammation is still largely unclear. In this review, we discuss recent reports regarding IL-17 cytokine family and Th17 differentiation pathways and how the IL-17-driven inflammation regulates allergic immune responses.

IL-17 cytokine family

Since the identification of IL-17A (originally named as CTLA-8) from activated T cell clones [1–3], five additional family members were subsequently uncovered and designated as IL-17A-F [4–6] (Table I). IL-17A, the prototypic family member, is a disulfide-linked homodimeric glycoprotein that possesses characteristic cystein knot structure, similar to that found in TGF-β, and nerve growth factor [7]. Among the IL-17 cytokine family, the expression and functions of IL-17A, IL-17F and IL-17E (IL-25) are better characterized. IL-17F share the greatest similarity with IL-17A (55% identity), whereas IL17E (IL-25) are the most distant (17%) [8]. Unlike other IL-17 cytokine family members located in different chromosomes, *Il17a* and *Il17f* are syntenic on mouse chromosome 1 and human chromosome 6, suggesting that the regulatory regions may exist within the IL-17A/F locus to control their expression. Indeed, the promoters and conserved noncoding sequence regions of IL-17A and IL-17F genes undergo coordinated chromatin modifications, similar to those identified in the locus of Th2 cytokine genes [9]. Both IL-17A and IL-17F were found to be produced by activated memory T cells, but other members of IL-17 cytokine family are expressed by broad range of tissues.

Studies of IL17 receptor family (IL-17RA-E) revealed additional complexities of the regulations and biological functions of IL17 cytokine family (Table I). IL-17RA, the cognate receptor for IL-17A, is ubiquitously expressed [10]. However, the biological activity of IL-17 or IL-17F is dependent on the heterodimeric complex composed of IL-17RA and IL17RC [11]. IL-17RB serves as receptor for both IL-17B and IL-17E with higher binding avidity to IL-17E [12]. Most of IL17 receptor family members exhibit broad tissue expression and often exist as alternatively spliced isoforms with no transmembrane or cytoplasmic domains, thereby acting as soluble decoy receptors. The diverse expression patterns and regulations of IL-17 cytokine family and their cognate receptors suggest that this newly identified cytokine family may possess unique immunological functions and play important roles in the maintenance of homeostasis and the progression of immune disease.

Th17 cells

The delineation of the newly defined Th17 subset has changed the perspectives of immunologist and led to the revision of Th1/Th2 paradigm [13]. The attempt to characterize the IL-17-producing T cells isolated from rheumatoid synovium or induced by microbial lipopeptides has first led to the hypothesis that IL-17A may define a new subset of Th cells functioning on local inflammatory reaction [14;15]. Studies using IL-17-deficient mice or by neutralizing IL-17A activity demonstrated that IL-17-producing cells, not Th1 cells mediate inflammatory pathology in autoimmune models [16–18]. The finding that IL-23 (p19−/−), but not IL-12 (p35−/−) mice resistant to the development of joint autoimmune inflammation were due to the lack of IL-17-producing, not Th1 T cells provide the basis for the discovery of Th17 cell lineage [19–22]. Th17 cells are now defined by their production of IL-17A, IL-17F, IL-22, and to a lesser extent, tumor necrosis factor (TNF) and IL-6 [23]. The identification of RORγt as the master transcription factor for controlling Th17 differentiation has further support the notion that IL-17-producing cells represent the additional T helper cell lineage [24]. The requirement of cytokine milieu to induce Th17 cell differentiation between humans and mice has been controversial. Recent studies suggest that TGF-β is essential for the induction of RORγt expression in both humans and mice, the

addition of IL-6 plus IL-23 or IL-21 in mice, or IL-6 plus IL-1β or IL-21 in humans triggers the production of IL-17A *in vitro* [25–29]. Interestingly, the additional complexity of the regulation of Th17 cells exits. The combination of IL-23 with TGF-β and IL-6 was found to be important for the maintenance of inflammatory Th17 cells *in vivo* by downregulating IL-10 production [30], whereas the addition of IL-27 with TGF-β and IL-6 lead to the suppression of Th17-mediated inflammation by the upregulation of IL-10 and IFN-γ production [31]. The identification of Th17 subset and the analyses of their functions have led to the resolution of some inconsistencies found in the Th1/Th2 paradigim. Th17 cells represent the third branch of $CD4^+$ Th subset and functions in the induction of tissue inflammation and host protection against extracellular pathogens. Understanding the cytokine milieu that regulates Th17 differentiation and effector function during allergic inflammation may be the key to control the pathogenesis of allergic diseases.

IL-17A potentiates allergic inflammation by regulating innate immunity

In asthmatic patients, IL-17A expression was increased in the lungs, sputum, bronchoalveolar lavage (BAL) fluids or sera, and the severity of airway hypersensitivity in patients correlates with the level of IL-17A expression, suggesting that IL-17 cytokines play important role on driving allergic inflammation [32]. Indeed, IL-17A and/or IL-17F can orchestrate local inflammation by inducing the release of proinflammatory cytokines such as TNF-α, IL-1β, G-CSF, and IL-6, as well as chemokines CXCL1/Gro-α, CXCL2, and CXCL8/IL-8 production by human bronchial fibroblast, epithelial, and airway smooth muscle cells, as well as venous endothelial cells *in vitro* [33]. Furthermore, IL-17A can act in synergy with IL-6 to induce mucus proteins (MUC)5B and MUC5AC [34], or with IL-1β and TNF-α to enhance vascular endothelial growth factor expression [35]. In addition to stimulating airway structural cells, IL-17A, and IL-17F can also trigger innate effector eosinophils to release chemokine CXCL1/Gro-α, CXCL8/IL-8, and CCL4/MIP-1β. The combination of IL-17F and IL-23 can further stimulate the production of proinflammatory cytokines IL-1β and TNF-α by eosinophils [36]. The importance of IL-17A effect on driving lung inflammation has been further substantiated by the findings in animal studies. Overexpression of IL-17A or the administration of recombinant IL-17A in the lung results in the influx and accumulation of neutrophils associated with elevated level of CXCL1/Gro-α, CXCL8/IL-8, granulocyte colony-stimulating factor (G-CSF), and enhanced granulopoiesis [37;38]. Mice deficient in IL-17RA or IL-17A have marked diminished recruitment of neutrophils into the lung in response to a challenge with gram-negative pathogen or allergen [16]. Together, these studies demonstrate that IL-17A can trigger lung inflammation by stimulating innate immunity to mediate neutrophil recruitments, implicating the potential role of IL-17A on the pathogenesis of severe asthma mediated by neutrophilia.

Atopic asthma features the infiltration and accumulation of Th2 effector/memory cells, eosinphils, and mast cells, and increased IgE productions. The role of IL-17A on Th2-driven allergic immune response has been complicated. In the studies using IL-17A−/− or IL-17RA −/− mice, IL-17A was found to contribute to the induction of allergen-specific Th2 cell activation, eosinophil accumulation, and serum IgE production [16;39]. On the contrary, the administration of neutralizing anti-IL17A mAb in ovalbumin (OVA)-challenged murine asthma model in the late effector phase induced the elevated eosinophil recruitment and IL-5 productions in BAL, suggesting a regulatory role of IL-17A on the established Th2-driven allergic immune response [39]. These studies demonstrate the effect of IL-17A on the onset of lung inflammation, which facilitates the Th2-driven pathogenesis of allergic asthma. Since no evidence showed the direct effect of IL-17A on Th2 cells, the observation that endogenous IL-17A can dampen Th2-driven eosinophil recruitment and IL-5 production in the late phase of allergic immune responses remain further investigation.

IL-25 enhances allergic inflammation by regulating adaptive immunity

Distinct from other IL-17 cytokine family members, IL-25 (IL-17E) was first described as a T_H2 cell-derived cytokine [40]. However, expression of IL-25 transcript was later found in mast cells activated by IgE cross-linking [41], alveolar macrophage and lung epithelial cells stimulated with allergens in mice [42]. In humans, bioactive IL-25 protein was found to be secreted by activated eosinophils and basophils [43]. Interestingly, these cells obtained from allergic patients produce more prominent amount of IL-25 after activation. These studies suggest that the primary cellular sources of IL-25 may exit in the branch of innate immunity.

In addition to low sequence homology and unique expression pattern, IL-25 also possess unique functions on evoking type 2 immune responses in animal studies [40;44;45]. Systemic administration of IL-25 protein [40;45] or overexpression of IL-25 [44;46] induces elevated T_H2 cytokine and eotaxin production, which results in eosinophilia, increased serum IgE, mucus hyperplasia, and other pathological changes in many tissues. Moreover, administration of a neutralizing antibody against IL-25 in an experimental model of allergic asthma resulted in significantly reduced levels of IL-5, IL13 production, serum IgE production, the infiltration of Th2 cells and eosinophils, and prevented airway hyperresponsiveness [47]. These *in vivo* studies imply that IL-25 may play a pivotal role in the development of Th2-mediated allergic inflammation.

The function of IL-25 on type2 immunity, which play protective role in defense against parasitic infection was further elucidated by recent studies in animal models using helminth infection. In the absence of IL-25, mice infected with *Trichuris muris*, the gastrointestinal parasite, failed to develop a lymphocyte dependent protective type2 immunity to expel chronic parasitic infection [48]. In the other study, IL-25 was found to trigger the non-B/non-T, c-kit$^+$ cells for the rapid clearance of *N. brasiliensis* acute infection [49]. Using allergen-induced allergic animal models, one study showed that administration of recombinant IL-25 proteins can induce acute lung inflammation mediated by the unidentified IL-5-producing non-B/non-T cells [45], whereas the other demonstrated that enforced expression of IL-25 in lung resulted in the amplification of allergic inflammation driven by CD4$^+$T cells and STAT6 signaling pathway [50]. These findings suggest that depending on experimental models, IL-25 can enhance type2 immune responses by regulating CD4$^+$ T cells or non-B/non-T, c-kit$^+$ cells.

The finding that IL-25 receptor (IL-25R or IL-17BR) is highly expressed on CD4$^+$ Th2 memory cells in humans has provided direct evidence that IL-25 can function directly on CD4$^+$ T cells to mediate enhanced type2 immune response [43;51]. Indeed, IL-25 costimulates the proliferation of the T_H2 memory cells, and enhances their T_H2 polarization and cytokine productions, in particular IL-5, by upregulating the gene expression of the transcription factors, *GATA-3*, *c-MAF*, and *junB* in an IL-4 independent manner [43]. In a parallel study in mouse, IL-25 treatment during T cell differentiation can enhance Th2 cytokine production, and inhibit IFN-γ production, indicative of the Th2 polarizing function [42]. Together, these results suggest that IL-25 may amplify allergic immune response by inducing Th2 differentiation and the local expansion and augmented effector functions of Th2 memory/effector cells. On the contrary to the T cell derived proinflammatory cytokine, IL-17A/F, which regulates the innate effectors or structural cells during the onset of allergic inflammation, IL-25 (IL-17E) produced by innate effectors, such as eosinophils, and basophils may exert a critical role in maintaining the functional capacity and homeostatic maintenance of IL-25R-expressing allergen-specific Th2 memory cells, thus propagating a positive feed back loop between innate effectors and adaptive immunity leading to the amplification of allergic inflammation. (Fig.1)

Conclusion

Tissue inflammation is often one of the characteristic features of allergic diseases. Studies of IL-17 cytokine family and Th17 cells have advanced our understanding of cellular mechanisms underlying allergic inflammation. Th17 cells can mediate tissue inflammation by the induction of chemokines and proinflammatory cytokines in the structural cells, thereby supporting neutrophil recruitment and survival. However, the introduction of this third branch of adaptive immunity also raises new questions as to how Th17 cells and Th2 cells cooperate in the pathogenesis of allergic diseases, such as asthma. Severe asthma caused by neutrophilia can be further classified into the eosinophilic or noneosinophilic asthmatics, suggesting that the heterogeneity in the pathology of asthma may be the results of the interplay between these two T cell subsets. Moreover, recent studies support a hypothesis that a reciprocal relationship between regulatory T cells and Th17 differentiation pathway may exist [27], adding further complexity to the immune regulation during allergic inflammation. Thus, the approaches to design curative therapy for chronic allergic diseases in a phase-specific manner may require not only the understanding of the factors that drive the various T helper subsets, but also their temporal sequence and potential interaction in the induction of immunopathology.

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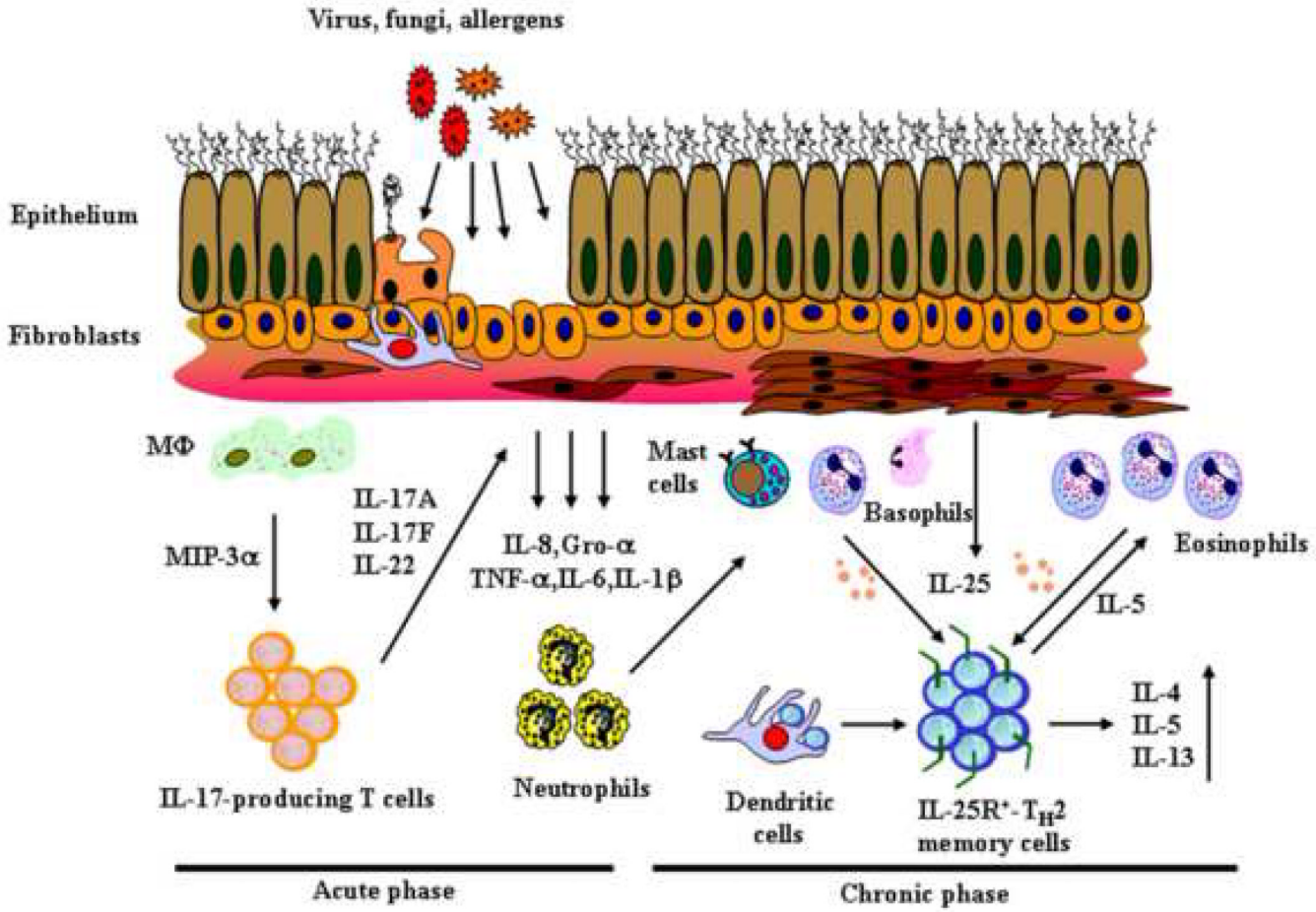

Fig. 1.

Table I

IL-17 cytokine family and functional effects on allergy

Ligands	Receptors	Functions	References
IL-17A	IL-17RA	IL-6, IL-8, IL-11, Gro-α, G-CSF and GM-CSF ↑	[38]
IL-17F	IL-17RA/C	*MUC5AC* and *MUC5B* ↑	[34]
		Airway hyper-reactivity ↑	[16]
		Neutrophilia ↑	[33]
		Severity of asthma ↑	[16]
IL-17E	IL-17RB	IL-4, IL-5, IL-13, IgE, and eotaxin ↑	[40,42,43,44,45,46,50]
		Mucus secretion ↑	[44,45]
		Airway hyper-reactivity ↑	[40,47,50]
		Eosinophilia ↑	[40,42,44,50]
		Severity of asthma ↑	[40,44,47,50]