Published in final edited form as:

Cytokine Growth Factor Rev. 2010 December ; 21(6): 413–423. doi:10.1016/j.cytogfr.2010.10.002.

IL-17 family member cytokines: regulation, and function in innate immunity

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Abstract

Recently, the IL-17 family member cytokines have become prominent subjects of investigation. IL-17 (IL-17A) is the best-described member of this family where its production has been mainly attributed to a specialized T helper subset of the adaptive immune response termed Th17. However, recent research on this and other Th17 cytokines has revealed new sources and functions of IL-17 family members in the innate immune response. This review will highlight recent advances in the field of IL-17 family member cytokines and will predominately focus on the innate regulation and function of IL-17, IL-17F, and IL-25.

Keywords

IL-17; IL-17F; IL-25; innate immunity

1. Introduction

The IL-17 family of cytokines consists of six family members of varying homology and function: IL-17 (also called IL-17A), IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F. In general, these cytokines range from 20–30 kDa and incorporate four conserved C-terminal cysteine residues (1,2). The cytokines IL-17 and IL-17F share the strongest homology, which is likely the reason why these mediators are thought to use similar signaling mechanisms in exerting their pro-inflammatory functions(1,3,4). Little is known about the regulation and function of IL-17B and IL-17C; however, there is some evidence that these cytokines are also regulators of the inflammatory response as well(5–7). IL-25 has the least homology with IL-17A, which may translate to its unique abilities in regulating allergy and T helper (Th) 2 responses (8–10). A summary of the known sources and functions of the IL-17 family of cytokines is presented in Table 1.

The cytokines IL-17 and IL-17F have been associated with a distinct lineage of CD4+ T helper lymphocytes (Th) known as Th17 cells (11,12). However, recent reports have

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strongly suggested that IL-17 and IL-17F expression is not strictly limited to Th17 cells or for that matter T cells at all. Additionally, the sources of IL-25 include both innate immune cells as well as cells from non-hematopoietic origins. Thus, this review will highlight recent developments in IL-17A, IL-17F, and IL-25 biology, with a special emphasis on the innate sources and functions of these cytokines.

2. IL-17 and IL-17F

IL-17 has been extensively studied since its discovery in human peripheral blood (13,14). The identification of IL-17 led to the unearthing of the specialized Th17 subset that was found to produce the cytokines IL-17 as well IL-17F (15–17). Upon recognition of cognate ligands, naïve CD4⁺ helper T (Th) cells differentiate into various effector lineages that can be characterized by the induction of specialized transcription factors and their subsequent patterns of cytokine expression. Naïve Th cells, however, do not simply autonomously decide their fate; environmental signals present during the initial activation events instead determine their effector properties (18,19). These environmental factors, produced by innate cells following host insult, are crucial for Th17 lineage commitment and maintenance and include transforming growth factor beta (TGFβ), IL-6, IL-1β, and IL-23 (17,20). However, the hallmark of inflammation is the rapid production of pro-inflammatory factors that are vital in the recruitment and activation of infiltrating leukocytes with the overall goal of combating host insult (21). Therefore, due to the known importance of IL-17 and IL-17F in the promotion of inflammation, there are likely many other sources of these cytokines, including the innate arm of immunity, which would provide a rapid means for IL-17 effector function.

2.1. The pro-inflammatory function of IL-17A and IL-17F

IL-17F was also discovered through homologous IL-17 sequence comparison in humans following the identification of IL-17 (4,22). Both IL-17 and IL-17F readily form homodimers, however, there is evidence that suggests that an IL-17/IL-17F heterodimer forms as well, where IL-17, IL-17F, or IL-17/IL-17F bind to ubiquitously expressed receptors, IL-17RA, IL-17RC, or IL-17RA/IL-17RC, respectively (1,23–26). The cytokines IL-17 and IL-17F employ the adaptors TRAF6 and Act1 in their signaling transduction pathways as well (27,28). Both IL-17 and IL-17F readily activate innate and tissue resident cells, such as fibroblasts and epithelial cells, to induce the production of pro-inflammatory cytokines and chemokines (reviewed in (29)). Although somewhat redundant in function, research has shown that in some cases IL-17F is less potent compared to IL-17 in activating target cells to produce pro-inflammatory products (30). Moreover, other pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNFα), have been shown to cooperate with IL-17 to synergistically enhance the inflammatory capacity of innate cells (31,32). Overall, one of the major outcomes attributed to considerable IL-17 and IL-17F production is the recruitment and subsequent activation of neutrophils during inflammation (3).

In vivo, IL-17 and IL-17F perform a wide variety of immunoregulatory roles during infection. For example, IL-17 production is readily induced following infection with the extracellular bacterium, *Klebsiella pneumoniae* (33–35). In humans, *Pseudomonas aeruginosa* infection stimulates IL-17 and IL-17F production (36). Blocking IL-17 during fungal infection, such as that observed in a model of *Pneumocystis carinii*, leads to exacerbated disease (37). Taken together, these examples along with many other studies (extensively reviewed in (29)) demonstrate the importance of IL-17 and IL-17F in combating microbial infections, through the activation of innate cells as well as the recruitment of inflammatory leukocytes.

Besides infection, one of the most prominent roles associated with IL-17 and IL-17F production is in the regulation of autoimmunity, where dysregulation of Th17 and other IL-17-producing cells may lead to severe disease. During multiple sclerosis (MS), Th17 cells and their associated cytokines have been shown to be critical for lesion development and central nervous system (CNS) inflammation (15,38,39). In contrast, the mouse model of human MS, experimental autoimmune encephalomyelitis (EAE) still develops, albeit partially, in mice lacking IL-17 expression (reviewed in (29)). This evidence suggests that although IL-17 is important during EAE pathogenesis, it is not the sole pro-inflammatory mediator contributing to CNS inflammation. Moreover, in models of rheumatoid arthritis, both IL-17 and IL-23 have been implicated in joint destruction (40–42). Blocking IL-17 following arthritis induction results in a protective effect (43). Furthermore, IL-17 deficiency results in a similar protection in other autoimmune inflammatory disease models, including colitis (44), and IL-17 and IL-23-producing cells have known roles in promoting psoriasis (45–48).

2.2. Differential regulation and function of IL-17A and IL-17F

Research into the differential regulation requirements for IL-17 and IL-17F to date has been minimal. However, there is one such report that suggests that inducible T cell kinase (Itk) expression, an important mediator for T cell receptor (TCR) signaling, is required for IL-17 induction (49). Ikt-deficient T cells had impaired ability to produce IL-17 but not IL-17F, even though Ikt levels did not influence ROR γ activity. Further analysis revealed that the promoter for IL-17 contained an NFATc1 binding site but the IL-17F promoter did not, providing mechanistic insight into this differential regulation. Thus, IL-17 and IL-17F are not always necessarily induced in the same manner, where further examination is needed to determine what other factors can regulate IL-17 or IL-17F-specific responses.

Although IL-17 and IL-17F are generally accepted to have redundant functions in promoting inflammation, there are a few prominent examples of differential functions of these highly related cytokines. In a seminal paper by our group, we examined many different aspects of IL-17 and IL-17F function (30). For example, IL-17F, like IL-17, was able to induce inflammatory molecules from MEF cells in vitro, however IL-17F was not nearly as effective when MEF cells were stimulated at similar concentrations of IL-17 and IL-17F. In vivo, IL-17 was shown to be critical in the early priming phase of EAE, possibly through the regulation of IFN γ -producing cells, whereas IL-17F was almost dispensable. In an allergic airway inflammation model, IL-17F-deficient animals, but not IL-17 $^{-/-}$, exhibited substantially decreased CXCL5 expression, which corresponded to reduced neutrophils. Conversely, in a mouse model of asthma IL-17-deficient animals exhibited a reduction of cellular infiltrates into the airways, most notably eosinophils. However, IL-17F-deficient mice exhibited the opposite phenotype; high levels of IL-5 and IL-13 in the airways were observed and subsequent eosinophil infiltration was greatly increased compared to wild-type and IL-17-deficient animals. Using the DSS-induced colitis model, our group also observed that IL-17-deficient mice had exacerbated disease compared to a milder phenotype in IL-17F $^{-/-}$ animals. Finally, human epidermal keratinocytes induced IL-8, a cytokine important for the development of psoriatic lesions, upon stimulation with IL-17F but not IL-17, suggesting a more prominent role for IL-17F in psoriasis (50,51). Taken together, these studies demonstrate that although these cytokines are somewhat redundant in promoting inflammation, these individual factors do in fact have unique effector functions depending on the environment and the nature of host insult.

3. IL-17 and IL-17F in innate immunity

As previously mentioned, the production of IL-17 and IL-17F has largely been attributed to specialized Th17 cells residing in the adaptive arm of immunity (17). However, a vast array

of exciting research performed in the past few years has concretely demonstrated that Th17 cells are just one of many sources of both IL-17 and IL-17F (Table 2). Not only do certain components of the innate immune response readily produce Th17 cytokines (IL-17, IL-17F, IL-22), they can be the predominate source of these cytokines in an assortment of disease settings. The most famous example of IL-17-producing innate cells to date is the innate-like $\gamma\delta$ T cell, however, additional known IL-17 and IL-17F innate producers will be discussed as well.

3.1. $\gamma\delta$ T cells

The $\gamma\delta$ T cells are a relatively specialized population, comprising 1–5% of the total lymphocyte fraction in humans and mice (52). $\gamma\delta$ T cells represent the first wave of T lymphocytes generated in ontogeny, where the presence of IL-7 in the thymus is crucial to their survival and expansion. Indeed, thymic precursors expressing high levels of IL-7 receptor are more likely to develop into $\gamma\delta$ T cells. As fetal maturation proceeds, the number of $\gamma\delta$ TCR-expressing cells remains constant as $\gamma\delta$ TCR-expressing cells dramatically increase (52–54). Traditionally, $\gamma\delta$ T cells were thought to function in the innate immune response as a “first line of defense” against invading pathogens mainly due to their strategic localization in pockets of vulnerable tissues such as the gut, skin, and lungs. Additionally, $\gamma\delta$ T cells express common $\gamma\delta$ T cell scavenger receptors, Toll-like Receptors (TLRs), and apoptosis-promoting molecules such as FasL and NKG2D (55). However, $\gamma\delta$ T cells do undergo VDJ gene rearrangements, a major facet of adaptive immunity. Thus, it is now widely believed that $\gamma\delta$ T cells may function in the so-called “transitional response” at the crossroads of innate and adaptive immunity (52,56–58).

3.1.1. IL-17-producing $\gamma\delta$ T cells: development and cytokine regulation—

Recent studies have indeed shown that $\gamma\delta$ T cells have the ability to produce both IL-17 and IL-17F (59). However, for a while it was unclear if $\gamma\delta$ T cells exhibited functional plasticity in cytokine production or were generally restricted to either being IL-17 or IFN γ producers. An important study recently published by Jensen and colleagues has helped clarified this issue (60). The authors first demonstrated that the commitment towards IL-17 or IFN γ production was determined during the thymic selection process for $\gamma\delta$ T cells. Cells that had previously interacted with antigen, the so-called “experienced cells”, demonstrated an IFN γ -producing phenotype. Conversely, naïve $\gamma\delta$ T cells leaving the thymus were primarily IL-17 producers. Furthermore, IL-17- and IFN γ -producing $\gamma\delta$ T cells also express the Th17 and Th1 transcriptional factors ROR γ and T-bet, respectively (61,62). Another recent report demonstrated that during thymic selection, CD27+ $\gamma\delta$ T cells exhibit high levels of T-bet and subsequently become IFN γ producers. In contrast, $\gamma\delta$ T cells lacking CD27 expression had constitutive levels of ROR γ and became IL-17-producing $\gamma\delta$ T cells (62). Finally, IL-17-producing $\gamma\delta$ T cells exhibit high expression of CCR6, a common marker present on Th17 cells (63,64). Thus, $\gamma\delta$ T cells are programmed to produce certain cytokines during developments and can be easily identified based on certain IL-17-producing or IFN γ -producing markers.

Th17 cell differentiation and maintenance involves various cytokines, with known roles of IL-6, TGF β , IL-1, IL-21, and IL-23 in this process (17,20). Thus, many researchers have questioned whether IL-17-producing $\gamma\delta$ T cells are governed by a similar set of factors. Interestingly, IL-6 does not appear to be a critical factor for the development of IL-17- and IL-17F-producing $\gamma\delta$ T cells (reviewed in (65)). In contrast, TGF β was recently demonstrated to be a pivotal factor for the development of $\gamma\delta$ T cells in the thymus (66). The role of IL-23 in promoting IL-17 responses by $\gamma\delta$ T cells is well established (59). Indeed, IL-23 receptor expression is a hallmark of IL-17-producing $\gamma\delta$ T cells (67). Moreover, $\gamma\delta$ T cells express IL-1 receptor, where treatment of this subset with a combination of IL-1 and

IL-23 readily induces IL-17 and IL-17F cytokine production in a TCR-independent manner (68). IL-21 is an autocrine factor necessary for the maintenance of Th17 populations (69). In the case of $\gamma\delta$ T cells, IL-21 has been discovered to expand human $\gamma\delta$ T cell populations (70,71), and is also important for $\gamma\delta$ T cell for the development of IL-17-producing $\gamma\delta$ T cells (69). Finally, although IL-23 is sufficient to induce IL-17 production from $\gamma\delta$ T cells alone, a synergistic effect of inducing IL-17 production is observed when $\gamma\delta$ T cells are treated with a combination of IL-23 plus TLR2 ligand (64). Moreover, our group has shown that treatment of IL-23 enhances the expression of TLR2 on $\gamma\delta$ T cells; whereas TLR2 but not IL-23 promotes proliferation of $\gamma\delta$ T cells. Finally, both TLR2 and IL-23-deficient $\gamma\delta$ T cells exhibit substantial defects in their ability to produce IL-17 in the periphery; however, both of these genes were not required for thymic development of IL-17-producing $\gamma\delta$ T cell populations (72). Therefore, IL-17-producing $\gamma\delta$ T cells do in fact incorporate many of the Th17-polarizing/maintenance factors to regulate cytokine production, however, it appears that these cells are utilizing these cytokines in a different context (i.e. the direct induction of IL-17 and IL-17F).

Th17 cells have well-defined transcription factors that are utilized for lineage commitment and cytokine production, including ROR γ , ROR α , IRF-4, and AhR (73–75). Consequently, research is now being directed to determine if IL-17-producing $\gamma\delta$ T cells utilize some if not all of the same transcription factors. As previously mentioned, IL-17-producing $\gamma\delta$ T cells do in fact utilize ROR γ (61,68). Furthermore, AhR is also enhanced in IL-17-producing $\gamma\delta$ T cells when stimulated with IL-23 and TLR2 ligand (64). Thus, there is some overlap in transcription factors utilized by Th17 and $\gamma\delta$ T cells, however the relative contributions of other factors such as ROR α and IRF-4 have yet to be determined. A comparison of Th and $\gamma\delta$ T cell cytokine commitment is presented in Figure 1.

3.1.2 IL-17-producing $\gamma\delta$ T cells: importance in disease— $\gamma\delta$ T cells are localized in mucosal tissues throughout the host to allow for the innate-like ability to rapidly produce immunoregulatory mediators, which is especially true of IL-17-producing $\gamma\delta$ T cells (59). In fact, it has been shown that $\gamma\delta$ T cells are crucial regulators of early inflammation and the dominant source of IL-17 and IL-17F in many disease models. For example, two recent publications eloquently demonstrated that IL-17-producing $\gamma\delta$ T cells were critical in the early stages of defense against *Listeria monocytogenes* infection (76,77). $\gamma\delta$ T cell-deficient mice were also found to have more severe skin lesions as a result of *Staphylococcus aureus* infection, and that the lack of IL-17 production normally associated with this subset was the primary cause for this phenotype (78). Moreover, mouse models of *Mycobacterium* infection have demonstrated that not only are IL-17-producing $\gamma\delta$ T cells crucial in host defense; they are also the primary source of IL-17 during these infections (79,80). Finally, Shibata and colleagues published research that showed that in *Escheria coli*-induced peritonitis, resident $\gamma\delta$ T cells were responsible for rapid IL-17 induction and neutrophil recruitment in a TLR4-dependent manner (81). Thus, this specialized subset of $\gamma\delta$ T cells clearly plays a key role in the control of bacterial infection.

In addition to critical protective roles in the early response to infection, IL-17-producing $\gamma\delta$ T cells may be critical for the development of autoimmune inflammatory disorders as well. Depletion of $\gamma\delta$ T cells prior to EAE induction led to drastically reduced EAE development and subsequent CNS inflammation (82). Moreover, recent reports have demonstrated that IL-17-producing $\gamma\delta$ T cells are found in the CNS tissues of EAE mice (68,83). Conversely, one must also consider the importance of the hallmark Th1 cytokine, IFN γ , in EAE pathogenesis. Wohler and colleagues have shown that IFN γ - and TNF α -producing $\gamma\delta$ T cells are critical as well for full EAE development (84). Although the function of IL-17-producing $\gamma\delta$ T cells in inducing EAE is somewhat undetermined, this specialized subset has additionally been linked to other CNS-related inflammatory disorders. For example, during

ischemic brain injury, $\gamma\delta$ T cells are the predominant source of IL-17 following activation in an IL-23-dependent manner (85). Finally, a recent study has shown the importance of IL-17 in experimental autoimmune uveitis, where IL-17-producing $\gamma\delta$ T cells were key mediators in the activation of autoreactive IL-17-producing $\alpha\beta$ T cells (86). Overall, recent evidence has suggested a function of these innate IL-17 generators in autoimmunity, however further experimental validation is needed to fully understand the regulation and function of this subset.

3.2. Lymphoid tissue inducer cells

Fetal lymphoid tissue inducer cells (LTi) are critical mediators for the development of lymphoid tissues (reviewed in (87)). Furthermore, LTi cells are related to certain types of natural killer (NK) cells in terms of development and surface molecule expression (88). LTi-like cells are found in adult spleen and share many of the same characteristics as LTi cells. LTi-like cells express high levels of OX40 ligand and have previously been shown to be major producers of innate IL-22 (89). LTi cells express ROR γ as well and most likely rely on this transcription factor to induce innate IL-17 expression (90). Additionally, LTi-like cells expressing IL-23R, AhR, and CCR6 will rapidly produce IL-17, IL-17F, and IL-22 in an innate capacity when stimulated with IL-23 along with the TLR2 ligand zymosan (91). Therefore, as recently described for $\gamma\delta$ T cells, a combination of innate-derived IL-23 with an innate-activation signal (TLR2) can lead to rapid IL-17 production in non- $\alpha\beta$ T cells. However, other factors such as potential contributions of additional Th17-polarizing cytokines and transcription factors as well as the physiological relevance of IL-17 and IL-17F production in LTi and LTi-like cells needs to be further addressed.

3.3. Natural Killer and Natural Killer T cells

NK cells are innate cells that function in two distinct capacities: 1) cytotoxic ability through granzyme and death receptor expression and 2) cytokine production to activate other immune cells. NK cells utilize both activating and inhibitory receptors to regulate their potent functions, where activating receptors recognize danger signals and inhibitory receptors recognize normal healthy conditions (reviewed in (92)). A role for NK cells in exhibiting certain Th17-like factors has previously been described. In certain situations NKp44+ NK cells produce high levels of innate IL-22 (93). Additionally, NK cells can express high levels of the transcription factor ROR γ (94). Thus, it seems plausible that NK cells would be another innate source of IL-17 and IL-17F, especially considering their developmental similarity to LTi cells. However, only one report has demonstrated that NK cells have this potential. In a model of toxoplasmosis, NK cells were able to generate IL-17 through a mechanism that was dependent on IL-6 (95). Thus, further assessments of NK cells as IL-17 producers are warranted.

Natural killer T cells (NKT) are class of T lymphocytes that express NK cells markers such as NK1.1 and that recognize lipid antigens presented by antigen presenting cells on the CD1d molecule. NKT cells can be divided into different categories based on TCR expression and reactivity to the ligand α -galactosylceramide (α GalCer) (reviewed in (96)). Of particular importance are the invariant NKT cells (iNKT) that express a single restricted TCR receptor and are activated by α GalCer. These cells were also shown to produce IL-17 in an innate capacity following TCR ligation and IL-23 stimulation (97). iNKT cells did not, however, require IL-6 to induce IL-17. Furthermore, CD4-/NK1.1+ NKT T cells were recently described as being the most potent IL-17 producers compared to the CD4+ and NK1.1+ NKT subsets (98). As in the case of other recently identified sources of innate IL-17, the factors regulating the production of IL-17 needs to be further examined. For example, IL-1 can induce NKT expansion (99) and NKT cells highly express the IL-21

receptor (100). Thus, it would be interesting to examine if these cytokines can influence IL-17 production in NKT cells.

3.4. Macrophages

Macrophages have been shown in a few reports to produce IL-17 under special circumstances as well. However, the signaling pathways utilized by macrophages for the innate production of IL-17 remain largely unknown. One such example came from testing for the presence of IL-17 in human breast cancer tissues. The authors found that CD68-stained macrophages also stained positive for IL-17 by histology (101). Moreover, in mice IL-17 production was demonstrated following chitin stimulation in a TLR2-dependent manner (102). Likewise, Song and colleagues provided evidence suggesting that IL-17 production can be dominated by alveolar macrophages in a model of allergic inflammation (103). However, a recent report has suggested that while IL-17F may be present in macrophages and other innate immune cells, IL-17 is mostly limited to T cells (104).

3.5. Additional innate sources of IL-17A and IL-17F

Paneth cells are granular epithelial cells that function in an innate capacity to produce antimicrobial products along with pro-inflammatory cytokines such as TNF α (reviewed in (105)). Recently, Paneth cells were found to contain large intracellular stores of IL-17 that could be rapidly released following TNF α stimulation (106). TLR5, an innate receptor recognizing bacterial flagella, was found to induce IL-17 from **CD3-/CD127+ cells** residing in the spleen and mucosa in a dendritic cell-dependent manner (107). These cells may represent an L T_i -like subset, as they are similar to L T_i and NK cells but lack the expression of ROR γ . **Neutrophils**, being a major recruitment target of IL-17 and IL-17F activation in innate cells, seem to be an unlikely source of IL-17. However, a recent paper that focused on a mouse model of ischemia-reperfusion injury suggests otherwise. IL-17-producing neutrophils are present within three hours following injury and likely depend on IL-23 (108). Additionally, *Bordetella pertussis* infection was shown to induce IL-17 production from infiltrating neutrophils, macrophages, and T lymphocytes (109). **Epithelial cells** have been shown to be an innate source of IL-17F but not IL-17 in the lung and colon (104,110). Finally, **mast cells** were recently shown to be a dominant source of IL-17 in human arthritis; mast cells relied on ROR γ and produced IL-17 following activation with pro-inflammatory cytokines or TLR signal (111). Additional analysis of these cell types will further our understanding of the innate immune system and IL-17 production.

3.6. Innate mechanisms regulating Th17 cells

Although strictly members of the adaptive arm of immunity, CD4+ and CD8+ T lymphocytes as well as B cells also express various members of the innate, evolutionary-conserved TLR family (reviewed in (112) and (113)). Therefore, our group analyzed the direct role of TLR signaling in Th17 maintenance and function (72). We found that TLR2 was enhanced in the Th17 lineage compared to the Th1 and Th2 subsets. Ligation of TLR2 led to a costimulatory effect in polarizing Th17 cells as well promoting their expansion. In vivo, the lack of TLR2 expression directly on CD4+ T cells led to reduced Th17 generation and an almost complete protection from the development of EAE. Furthermore, we demonstrated that CD4+ T cells are likely activated by endogenous TLR2 ligands generated during the inflammatory process, which as of now are still undefined. Future studies should focus on other innate pathways that CD4+ T lymphocytes may utilize for IL-17 production, expanding our knowledge of direct innate regulation by molecules expressed by adaptive immune cells.

4. IL-17E (IL-25)

IL-25, a distinct cytokine in the IL-17 family was originally identified on the basis of searching for sequence homology to the other IL-17 family members (10,114). Seminal studies in renal carcinoma cell lines showed an effect of IL-25 in inducing the expression of the pro-inflammatory cytokine, IL-8 through NF- κ B activation (114,115). However, additional studies *in vivo* indicated that IL-25 plays vital roles in regulating type-2 immune response (115). While IL-17 and IL-17F induce neutrophilia, participate in immunity against certain bacterial and fungal infections, and are involved in the pathogenesis of multiple autoimmune diseases; IL-25 promotes eosinophilia and appears to play important roles in Th2-mediated host defense against helminthic parasite infection as well as in exacerbating allergic airway diseases.

4.1 The expression and regulation of IL-25

IL-25 was initially reported to be derived from highly polarized Th2 cells (10), but later on it was found to be expressed by several cell types both in the hematopoietic and non-hematopoietic compartment. IL-25 mRNA was expressed by IgE-activated mast cells (116), alveolar macrophages (117), microglia (118), eosinophils (119) (120), basophils (120), epithelial cells (121,122), and endothelial cells (123). In the brain, IL-25 mRNA is constitutively expressed by mouse microglia and by brain capillary endothelial cells and its expression is involved in protection from inflammatory brain diseases such as MS (118,123). In the gut, IL-25 can be found in the large intestine, in particular intestinal epithelial cells, and is involved in maintenance of intestinal homeostasis (122). In the lung, IL-25 was induced in mouse models of allergic lung disease (124). Our group has demonstrated that several allergens such as ragweed and fungal protease can induce IL-25 mRNA expression in lung epithelial cells (121). Therefore, IL-25 plays important roles in the pathogenesis of allergic lung disease and the tissue expression of IL-25 contributes to immune responses against pathogens and controls local inflammation.

Although many reports provide insight into which cells produce IL-25, the mechanisms governing the expression of this cytokine remain unclear. IL-25 can be detected in intestinal epithelial cells from conventionally reared mice, however, IL-25 expression is absent in the germ-free mice (122), suggesting that signals from gut pathogens can induce IL-25 expression. In the airway, IL-25 in lung epithelial cells can be induced by protease allergens (121,125). The induction of IL-25 by allergens was shown to be suppressed by Erk, JNK, and p38 inhibitors (125), suggesting that allergens can regulate the expression of IL-25 through the MAPK pathway. Furthermore, some airway epithelial cell-derived factors, such as matrix metalloproteinase 7 (MMP7), have been shown to modulate IL-25 function in the airway during allergic asthma (126). IL-25 can be cleaved by MMP7 at multiple sites and this processed IL-25 is better at inducing Th2 cytokine production compared to native IL-25 (126). Finally, viral infection was also found to induce the expression of IL-25 in lung tissue and that this IL-25 expression may contribute to virus-induced exacerbation of allergic asthma (127). Thus, signals from pathogens themselves may be capable of regulating IL-25 expression.

4.2 IL-25 receptor and target cells

The receptor for IL-25 was identified based on homology searches for sequences related to the IL-17 receptor. The IL-25 receptor was found to be the same receptor for IL-17B (termed IL-17RB or EV127); however, IL-25 was found to have a higher binding affinity to IL-17RB compared to IL-17B (114,128,129). Further studies by Rickel et al. found that the functional IL-25 receptor indeed requires not only IL-17RB but also IL-17RA, where mice deficient in either IL-17RA or IL-17RB did not respond to IL-25 (130). Similar to the IL-17

receptor that requires IL-17RA and IL-17RC complex, the interaction of both IL-17RA and IL-17RB is important for IL-25 activity. While IL-17 mainly functions on structural cells such as epithelial cells and fibroblasts to induce pro-inflammatory cytokines and chemokines, IL-25 mostly targets hematopoietic cells and induces the production of Th2 cytokines. Both innate and adaptive immune cells are currently known to be potential targets for IL-25.

Several IL-25 innate immune responder cells, including monocytes (119,131) and NKT cells (132,133) were reported to express functional IL-17RB and IL-25 treatment of these cells induced Th2 cytokine production. *In vivo*, IL-25 treatment in Rag knockout mice induced Th2 cytokine production from undefined populations of non-T/non-B (NBNT) cells (10). Recently, three groups independently identified a novel population of innate effector cells that are indeed innate IL-25 responders. These cells are responsible for the production of Th2 cytokines, in particular IL-13, during helminthic parasite infection and serve to mediate worm expulsion (134–136). These innate IL-25 responder cells were named accordingly to investigator preference: nuocyte by Neill et al. (134), MPP^{type2} cells by Saenz et al. (135), and ih2 cells by Price et al (136). Whether these cells are the same population and function in other Th2-associated diseases remains unclear.

Not only can IL-25 target innate immune cells to produce Th2 cytokines, it also can direct naïve T helper cells towards Th2 commitment as well as augment the cytokine production of effector/memory Th2 cells (120,121). IL-17RB mRNA was highly expressed in Th2 cells but not in Th1 and Th17 cells (121,137). Treatment of naïve T cells with IL-25 promoted the differentiation of Th2 cells in an IL-4 and STAT-6 dependent manner, but had no effect on the polarization of Th1 and Th17 cells. Furthermore, our group demonstrated that IL-25 could augment c1 and JunB transcription factors during early T cell differentiation, possibly resulting in upregulation of initial IL-4 levels (121). Moreover, the expression of IL-17RB can be detected in circulating human Th2 memory cells and further up-regulated in CD3/CD28-activated cells (120,138). Thymic stromal lymphopoietin (TSLP) is known to activate dendritic cells produce express Th2-polarizing signals and TSLP-activated dendritic cells can direct the differentiation of Th2 cells (139). In the presence of TSLP-activated dendritic cells, IL-17RB on Th2 memory cells was strongly induced and further IL-25 treatment enhanced their polarization and proliferation (120). Moreover, Th9 cells, a recently identified T helper lineage that produces mainly IL-9, was also found to express IL-17RB (137). Unlike Th2 cells, the differentiation of Th9 from naïve T cells is induced by TGF- β and IL-4 (140,141). Th9 cells demonstrated the highest expression of IL-17RB compared to other Th subsets and treatment of IL-25 on differentiating Th9 cells enhanced their IL-9 and IL-10 production (137). Enforced expression of IL-17RB by CD4⁺ T cells induced substantial production of IL-4, IL-5, IL-13, and IL-9, implicating the involvement of IL-25 function in not only Th2 but also Th9 differentiation (137). These data indicate that IL-25 may act on both innate responder cells and adaptive T helper cells to induce type-2 immunity.

4.3 Biological function of IL-25

IL-25 has been implicated in the regulation of type-2 immune responses. *In vivo* studies by IL-25 protein injection and in IL-25 transgenic mice showed the induction of eosinophilia and Th2 cytokine expression in several tissues (10,142,143). There have been many reports on the pathogenic roles of IL-25 in Th2-based diseases, especially those pertaining to allergic lung. IL-25 is not only linked to allergic disease, but also plays a protective role in helminthic parasite infection. Additionally, IL-25 functions in the regulation of some autoimmune diseases, such as EAE. The known roles of IL-25 in disease are summarized in Table 3.

4.3.1 Pathogenic roles of IL-25 in allergic lung diseases—Studies in both mice and humans have demonstrated the crucial roles of IL-25 in the pathogenesis of allergic lung diseases. Accordingly, the expression of IL-25 and IL-17RB has been detected in asthmatic lung tissues (120,124). In patients with allergic rhinitis, IL-25 and TSLP was found to be upregulated in nasal lavages (144). Overexpression of IL-25 in the lung epithelium of mice induced epithelial cell hyperplasia, mucus hyper-secretion, airway infiltration of eosinophils and macrophages, and the upregulation of chemokines associated with type-2 immunity (121). In contrast, IL-25 neutralization attenuated allergic inflammation with reduced eosinophils and CD4+ T cells in the airway (121). Moreover, mice treated with anti-IL-25 exhibited less Th2 cytokine production in bronchoalveolar lavage and reduced OVA-specific Th2 cytokine production in splenocytes (121). Likewise, IL-25-deficient mice showed significant attenuation of allergic inflammation, characterized by reductions in both Th2 and Th9 cytokines (137). Indeed, IL-25 appears to be important for both the sensitization and the challenge phase of airway responses (145). IL-25 blockade during the sensitization phase resulted in reduced levels of not only Th2 cytokines, but also goblet cell hyperplasia and serum IgE secretion (145). More importantly, neutralizing IL-25 either in the sensitization or the challenge phase can prevent airway hyper-responsiveness (AHR) (145). The induction of airway hyper-reactivity by IL-25 was dependent on IL-17RB-expressing NKT cells (132,133). Similarly, inhibition of the IL-25 and IL-17RB interaction through the use of soluble IL-17RB or an anti-IL-17RB in a mouse model of asthma resulted in reduced airway inflammation, hyper-reactivity, and airway remodeling (124,145). More recent studies have found enhanced expression of IL-25 in the lung following pneumonia virus infection, suggesting that IL-25 induced by early-life virus infection may promote further development of allergic airway responses (127). These data thus indicate the importance of IL-25 in promoting allergic lung disease and the IL-25 pathway may be a target of novel therapeutics in the future.

4.3.2 Protective roles of IL-25 in helminthic parasite infection—Helminthes are parasites known to induce strong type-2 immune responses. Recent data indicate that IL-25 strongly contributes to protective immunity against intestinal helminthic infection. The role of IL-25 in helminthic parasite infection has been examined in two different models thus far. In a mouse model of Trichuriasis (whipworm infection), exogenous IL-25 treatment induced a protective Th2 response and worm expulsion in genetically susceptible mice (9). In contrast, IL-25 knockout mice were unable to eradicate the infection. The mechanism by which IL-25 regulated worm protection in this model was shown to be lymphocyte dependent. During chronic infection with *Trichuris*, IL-25 was also able to ameliorate chronic inflammation and maintain mucosal integrity (9). Likewise, in hookworm *Nippostrongylus braziliensis* infection, IL-25 was shown to be involved in worm clearance (8). In IL-25-deficient mice, this worm could not be expelled efficiently, which correlated with a significantly reduced level of type-2 cytokines (8). Unlike whipworm infection, IL-25 seems to mediate worm expulsion independent of lymphocytes in *N. braziliensis*-infected mice. IL-25 treated-Rag knockout mice were still able to eradicate the worm (8). The mechanism of worm protection mediated by IL-25 in this mouse model was found to be dependent on NBNT cells (8). More recent work has clearly demonstrated that NBNT cells are indeed the novel innate type-2 effector cells responsible for the IL-25 effect in *N. braziliensis* infection (134–136). These studies indicate the essential function of IL-25 in protection to helminthic parasite infection. Whether IL-25 plays roles in other helminthic parasite infections or utilizes a similar pathway(s) for protection remains unclear.

5. Summary and conclusions

Although traditionally thought of as adaptive responders, Th17-related cytokines (IL-17 and IL-17F) have various innate sources and function as rapidly produced pro-inflammatory

mediators. Innate IL-17-producing cells also employ many of the cytokine and transcriptional regulators utilized by Th17 cells. Clearly, $\gamma\delta$ T cells have been shown to have important immunological consequences as a function of their IL-17 production. However, further research needs to expand on the regulation of IL-17, IL-17F, and IL-22 in this cell type. Moreover, the relative contributions of IL-17 and IL-17F expression from NK cells, LT α cells, and other hematopoietic and non-hematopoietic lineages needs to be more thoroughly addressed to determine the physiological relevance of their innate IL-17 production. The unifying factors of innate IL-17 and IL-17F production in various cell types include ROR family expression, IL-23 reactivity, and possibly TLR-mediated activation.

Unlike IL-17 and IL-17F, IL-25 has unique functions in promoting type-2 immunity as well as inhibiting pro-inflammatory responses. IL-25, expressed by several innate immune cell types including mucosal epithelial cells, eosinophils, basophils, and mast cells, is capable of inducing Th2 cytokines from both innate and adaptive IL-25 responders. IL-25 can target innate immune cells, including NKT cells, monocytes, and NBNT cells, which are recently identified novel innate effector cells that produce the initial Th2 cytokines during helminth parasite infection. IL-25 also can act on naïve T cells by promoting polarization toward the Th2 lineage and on memory/effector Th2 cells by enhancing their Th2 cytokine production. Additionally, a novel T helper lineage, Th9 can also respond to IL-25, which functions in augmenting IL-9 production. The effect of IL-25 on multiple cells can thus result in dysregulated Th2 responses in asthma, protective immunity to helminth infection, and pathological suppression of autoimmune diseases (Figure 2).

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Figure 1.

Differentiation pathways of CD4⁺ T helper cells compared to IL-17- and IFN_γ-producing γδ T cells. γδ T cells utilize many of the same cytokines and transcription factors as Th cells for the regulation of cytokine production. The primary difference between the development of cytokine-committed αβ and γδ T cells seems to be that this process occurs in the thymus in the case of γδ T cells compared to the periphery in CD4⁺ T helper cells.

Figure 2.

Many stimuli such as allergens or pathogens can induce several cell types to express IL-25. IL-25 functions on both innate effectors and adaptive T cells to promote type-2 immune responses. IL-25 plays pathogenic roles in allergic lung diseases and protective roles in helminth parasite infection and some organ-specific autoimmune diseases such as experimental encephalitis autoimmune disease (EAE) and colitis.

Table 1

The IL-17 family member cytokines

Cytokine	Receptor	Source	Known functions	Role in disease	References
IL-17A (IL-17)	IL-17RA, IL-17RC	CD4+ and CD8+ T cells, $\gamma\delta$ T cells, NKT cells, other innate cells	Induce pro-inflammatory cytokines and chemokines in various target cells which promote inflammation and neutrophil recruitment	Pro-inflammatory functions in host defense against extracellular bacteria, fungi, and possibly some viral infections and cancers. Promotes inflammation associated with autoimmunity	(11,15,17,59,146–148)
IL-17B	IL-17RB	Pancreas, gut, cartilage, neurons, embryonic limb buds	Stimulates TNF α and IL-1 β from monocytes; stimulates chondrocyte proliferation	Associated with arthritis; bone fracture healing	(5,7,149–151)
IL-17C	?	Prostate, kidney, psoriatic skin, pneumonia-infected lung	Stimulates TNF α and IL-1 β in THP-1 cells	Expression correlates with arthritis and psoriasis; upregulated following pneumonia infection	(5–7,26,152)
IL-17D	?	Nervous system, muscle, heart, adipose	Stimulates IL-6, IL-8, and GM-CSF from endothelial cells	Reduced in psoriasis	(152,153)
IL-17E (IL-25)	IL-17RB, IL-17RA	Epithelial cells, myeloid cells, eosinophil, basophil, mast cells	Induces Th2 cytokines in NBNT, monocytes and NKT cells; promotes Th2 differentiation, enhances Th9 differentiation	Promotion of type 2 helper responses in vivo, promotes allergic lung disease, important in host defense against parasites; possible roles in autoimmune inflammatory disorders	(8,9,114,118,120,121,130)
IL-17F	IL-17RA, IL-17RC	CD4+ and CD8+ T cells, $\gamma\delta$ T cells, epithelial cells and other innate cells	Induces pro-inflammatory mediator production in hematopoietic and non-hematopoietic cells (less potent than IL-17A), involved in neutrophil recruitment, induces IP-10 from bronchial epithelial cells	Similar pro-inflammatory functions to IL-17; not as important as IL-17A in EAE; inhibitory in asthma and colitis; potent in psoriasis	(1,11,17,30,50,154,155)

Table 2

Sources of Th17-related cytokines in innate immunity

Source	Secreted cytokine(s)	Induction signals	Transcription factors	Role in disease	References
$\gamma\delta$ T cell	IL-17, IL-17F, IL-22	IL-1, IL-23, TLRs, TGF β	ROR γ , AhR	Prominent during bacterial infection (i.e. <i>Staphylococcus</i> and <i>Mycobacterium</i>); potential roles in autoimmunity	(63–66,68,78,79,83)
LTi and LTi-like cells	IL-17, IL-17F, IL-22	IL-23, TLR2	ROR γ , AhR	Rapid IL-17 responses; specific pathogens?	(89–92)
NK cells	IL-17, IL-22	IL-6	ROR γ , AhR	Toxoplasmosis	(93–95)
NKT cells	IL-17, IL17F?	IL-23	ROR γ	Rapid IL-17 responses, specific pathogens?	(97,156)
Macrophages	IL-17	Chitin	?	Breast cancer, allergic inflammation	(101–103)
Paneth cells	IL-17	TNF α + pattern recognition receptor	?	Gut immunity	(106)
Neutrophils	IL-17	Pathogen product?	?	Ischemia-reperfusion injury; <i>Bordetella pertussis</i> infections	(108,109)
Epithelial cells	IL-17F	Pathogen product?	?	Lung and colon immunity	(104,110)
Mast cells	IL-17	TLR	ROR γ	Arthritis	(111)

Table 3

The role of IL-25 in disease

Disease	Evidence in human/mouse	Source of IL-25	IL-25 target cells	Role in disease	References
Allergic rhinitis/asthma	Human, mouse	Epithelial cells, Eosinophils, Basophils, Mast cells	Th2 cells, Th9 cells, NKT cells, Monocytes	Induce Th2 cytokines, lung inflammation Induce lung remodeling and AHR Exacerbate diseases	(121,125,137,144,157)
Autoimmune disease (EAE)	Mouse	Microglia, Brain capillary endothelial cells	?	Induce Th2 cytokines, Suppress Th17 cytokines, Inhibit EAE development Maintain blood brain barrier integrity	(118,123)
Colitis	Human, mouse	?	CD14+ cells	Inhibit pro-inflammatory cytokines, Protective role in colitis	(158,159)
Helminth parasite infection	Mouse	?	NBNT cells	Induce Th2 cytokines Induce worm clearance limit chronic inflammation	(8,9,134–136)