

# Molecular mechanisms in allergy and clinical immunology

Series editors: William T. Shearer, MD, PhD, Lanny J. Rosenwasser, MD, and Bruce S. Bochner, MD

## IL-17 cytokine family

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A new family of cytokines, IL-17, has recently been defined that reveals a distinct ligand-receptor signaling system. Functional studies have provided evidence for its importance in the regulation of immune responses. Notably, 3 members, IL-17A, IL-17E (IL-25), and IL-17F, have been best characterized both *in vitro* and *in vivo*, and have been shown to be proinflammatory in nature. This proinflammatory activity is exemplified by their involvement in pulmonary inflammatory responses, in which both IL-17A and IL-17F are involved in the recruitment of neutrophils, and IL-17E is able to induce T<sub>H</sub>2 cytokine production and eosinophilia. Although the elucidation of a detailed mechanism of action continues to be an active area of research, the potent inflammatory activity and its association with various human disease states suggest this new cytokine family as an important contributor to the pathophysiology of human disease conditions, in particular the pulmonary diseases. (J Allergy Clin Immunol 2004;114:1265-73.)

**Key words:** IL-17 family, IL-17A, IL-17E (IL-25), IL-17F

Cytokines are secreted proteins that regulate many biological activities, including hematopoiesis and immunity. The IL-17 cytokine family is a recently discovered group of cytokines. IL-17A, the original member of this family, was first identified in 1995<sup>1</sup> and was initially recognized for its similarity to a sequence belonging to open reading frame 13 of *Herpesvirus saimiri*. Subsequent functional analysis demonstrated its ability to induce the production of other cytokines and chemokines, such as IL-6, IL-8, and granulocyte colony-stimulating factor (G-CSF), from a variety of cell types, providing the basis for being a bona fide cytokine. Structurally, IL-17A has no sequence similarity to any other known cytokines or other

### Abbreviations used

BALF: Bronchoalveolar lavage fluid  
COPD: Chronic obstructive pulmonary disease  
ENA-78: Epithelial cell-derived  
neutrophil activating protein 78  
ERK: Extracellular signal-regulated kinase  
G-CSF: Granulocyte colony-stimulating factor  
GRO $\alpha$ : Growth-related oncogene  $\alpha$   
HUVEC: Human umbilical vein endothelial cell  
ICAM-1: Intracellular adhesion molecule 1  
IP-10: IFN- $\gamma$  inducible protein 10  
MCP: Monocyte chemoattractant protein  
MIP-3: Macrophage inflammatory protein 3  
NF $\kappa$ B: Nuclear factor  $\kappa$ B

mammalian proteins.<sup>2</sup> Also, its receptor, IL-17R, is not related to any of the other known cytokine receptors and does not possess any recognizable domains.<sup>2</sup> Thus, the IL-17 cytokine family appears to represent a distinct ligand-receptor signaling system.

In recent years, we have witnessed the explosion of novel gene discovery, a result in large part of the availability of human genome sequences and bioinformatics tools that have facilitated the gene discovery process. Indeed, 5 additional members of the *IL17* gene family were discovered primarily from the genome sequences within a short period between 2000 and 2002<sup>3-9</sup> and were sequentially named in the order of discovery. *IL17B* and *IL17C* were identified on the basis of a sequence similarity search of the expressed sequence tag database.<sup>4</sup> Similarly, 3 additional members, *IL17D*, *IL17E* (also called IL-25), and *IL17F* were discovered primarily on the basis of sequence homology search from the genomic DNA sequences. These molecules have a similar molecular weight of 20 to 30 kd and have overlapping, but not identical, biological activities. Although these new and exciting findings have been the basis for several recent reviews,<sup>10-12</sup> this review highlights the structural and functional features of the IL-17 cytokine family, particularly for the 3 best characterized members, IL-17A, IL-17E (IL-25), and IL-17F, and their involvement in pulmonary inflammatory responses.

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Disclosure of potential conflict of interest: None disclosed.

Received for publication September 21, 2004; revised October 15, 2004; accepted for publication October 18, 2004.

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2004.10.019

## STRUCTURAL CHARACTERISTICS

Alignment of the predicted amino acid sequence of IL-17A and the other members reveals that the highest overall amino acid sequence identity (50%) is found between IL-17A and IL-17F, whereas only 10% to 30% sequence identity is seen between IL-17A and the other family members. They bear greatest similarity within the C-terminal 70 amino acids and have 4 well conserved cysteines. The crystal structure of one of the family members, IL-17F, has been determined recently.<sup>9</sup> The 4 conserved cysteines in the C-terminal half of the IL-17F sequence are shown to form a cystine knot in the crystal structure,<sup>9</sup> and interestingly, this cystine knot structure is similar to a common structural motif seen in several growth factors, such as bone morphogenic proteins, TGF- $\beta$ , nerve growth factor, and platelet-derived growth factor. In addition, IL-17F is believed to form disulfide-bonded homodimers,<sup>9</sup> whereas other members of the IL-17 family are expressed as tightly associated dimers.

## EXPRESSION OF THE IL-17 CYTOKINE FAMILY

Members of the IL-17 cytokine family appear to have a very distinct expression pattern and are likely to have a distinct biological role. The original member of this family, IL-17A, is mainly expressed in CD4<sup>+</sup> T cells, but only on activation, with no expression seen in the resting state.<sup>2</sup> IL-17A-expressing T cells are not classified into either the T<sub>H</sub>1 or the T<sub>H</sub>2 subset.<sup>13-15</sup> Analysis of individual T-cell clones showed, however, that many IL-17-producing clones appear to represent a distinct cell population<sup>15</sup>; that is, they do not coexpress either T<sub>H</sub>1 (IFN- $\gamma$ ) or T<sub>H</sub>2 (IL-4 and IL-13) cytokines. Recent reports have indicated that in addition to the T cells, neutrophils, eosinophils, and CD8<sup>+</sup> T cells are sources of IL-17A.<sup>16-18</sup>

Two members of this cytokine family, IL-17B and IL-17C, are expressed in a wide range of tissues,<sup>3,4</sup> but the cell sources of IL-17B and IL-17C have not been identified. The *IL17D* gene appears to be most homologous to *IL17B* and is expressed widely in skeletal and heart muscle, brain, adipose tissue, lung, and pancreas.<sup>5</sup> The cellular source of IL-17D is resting CD4<sup>+</sup> T cells and CD19<sup>+</sup> B cells.<sup>5</sup> The expression of the *IL17E* gene is detected at very low levels in several tissues, including kidney, testis, lung, adrenal gland, brain, spinal cord, prostate, and trachea.<sup>6</sup> Unlike IL-17A, IL-17E (IL-25) expression is restricted to the T<sub>H</sub>2 cells,<sup>19</sup> and interestingly, mouse bone marrow-derived mast cells are also able to produce IL-17E after the cross-linkage of the receptor for IgE.<sup>20</sup>

The expression pattern of the last member of this family, IL-17F, is more complex than those seen for other members. Two different isoforms (the longer and the shorter forms) of human *IL17F* have been found. The mechanism in the regulation of the expression for the longer versus the shorter form of the *IL17F* gene remains

unclear but appears to be a result of differential splicing or the alternative usage of the translation start site.<sup>7</sup> On the basis of currently available data, no apparent functional difference has been noted between these 2 isoforms. Although both the longer and the shorter forms of the *IL17F* gene are expressed in activated CD4<sup>+</sup> T cells, increased gene expression of the shorter form is evident in additional cell types after activation, including peripheral blood basophils and cord blood-derived mast cells.<sup>7,9</sup> Also, the shorter form is expressed in allergen-specific CD4<sup>+</sup> T-cell clones with different cytokine phenotypes (T<sub>H</sub>0, T<sub>H</sub>1, and T<sub>H</sub>2 subsets). Although the T cells appear to be the major cell source for IL-17A, unresolved issues are whether the same T-cell population is also able to coexpress IL-17F and/or IL-17E, 2 additional members produced from activated CD4<sup>+</sup> T cells, and whether there is a differential expression of these cytokines in response to different stimuli. This is a piece of the puzzle awaiting further investigation. It is of interest to note that although there is a significant degree of sequence homology and functional similarity between IL-17A and IL-17F, several types of tissues, including liver, lung, ovary, and fetal liver, show only the expression of *IL17F*,<sup>7</sup> suggesting a wider tissue distribution and a more diverse biological function of IL-17F compared with IL-17A.

Several attempts have been made to investigate the regulatory pathways leading to the induction of these 2 cytokines, and the results have been informative. Currently, in addition to the antigen as an inducer for the expression of IL-17A, 2 monocyte/dendritic cell lineage-derived cytokines, IL-15 and IL-23, are important stimuli for the induction of IL-17A. IL-15 has been shown to be able to induce IL-17A from CD4<sup>+</sup> T cells and neutrophils,<sup>17</sup> and IL-23 is also critical for IL-17A production from both CD4<sup>+</sup> and CD8<sup>+</sup> T cells.<sup>21-23</sup> Similar to IL-17A, IL-17F is inducible in IL-23-stimulated mononuclear cells isolated from mouse spleens.<sup>21</sup> Both IL-15 and IL-23 have been shown to be important in memory development of the T cells,<sup>24</sup> and IL-23 is involved in innate immunity and mucosal T-cell response.<sup>25</sup> The ability of these 2 cytokines to induce IL-17A (and perhaps IL-17F) may thus serve as a bridge between innate and adaptive immunity, wherein the IL-17 cytokine members, IL-17A and IL-17F, are the principal effector cytokines.

## FUNCTIONAL ASPECTS

Investigation into the function of the IL-17 cytokine family has been extensive, but the majority of the effort has centered on the role of 3 members, IL-17A, IL-17E, and IL-17F, in immunoregulation. The fact that these 3 members of the IL-17 cytokine family are expressed in diverse cell types and tissues suggests a pleiotropic biological activity. Indeed, *in vitro* experiments using various target cell types and recombinant forms of cytokines have shown a wide variety of functions. Further, increased *in vivo* expression of these 3 members in various disease states

TABLE I. Summary of key functional features

| IL-17 family | Model                                       | Functional effect                                                                                                                    | Comment                                      | Reference |
|--------------|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-----------|
| IL-17A       | Bronchial epithelial cells                  | Increased expression of IL-6, IL-8, G-CSF, GM-CSF, and granulocyte chemotactic protein 2                                             | No effect on CC chemokine expression         | 27-29     |
|              | Bronchial epithelial cells                  | Increased expression of mucin genes                                                                                                  |                                              | 46        |
|              | Fibroblasts                                 | Increased expression of IL-6, IL-8, IL-11, and GRO $\alpha$                                                                          | Inhibited by dexamethasone                   | 48        |
|              | IL-17A-deficient mice                       | Decreased AHR                                                                                                                        |                                              | 50        |
|              | Mice (intratracheal instillation of IL-17A) | Decreased expression of IL-4, IL-5 and IgE                                                                                           |                                              |           |
|              |                                             | Induction of neutrophilia                                                                                                            | Via induction of IL-8                        | 34        |
|              | Mice (adenovirus-mediated gene transfer)    | Peripheral neutrophilia                                                                                                              | Lung neutrophilia not tested                 | 35        |
|              | Mice (treatment with anti-IL-17A mAb)       | Reduction of neutrophilia                                                                                                            |                                              | 36        |
|              | Mice (IL-17R-deficient)                     | Reduction of <i>K pneumoniae</i> -induced neutrophilia                                                                               |                                              | 55        |
|              | Mice (adenovirus-mediated gene transfer)    | Host defense and early survival after <i>K pneumoniae</i> infection; reduced bacterial growth                                        |                                              | 56        |
|              | Human (asthma)                              | Increased expression of IL-17A                                                                                                       |                                              | 18,48     |
|              | Human (asthma and COPD)                     | Increased expression of IL-17A correlates with AHR                                                                                   |                                              | 51        |
|              | Human (asthma)                              | Increased expression of IL-17A correlates with severity                                                                              |                                              | 18        |
| IL-17E       | Transgenic mice                             | Induction of AHR; High level of T <sub>H</sub> 2 cytokines, eotaxin, IgE, eosinophilia, and mucus hypersecretion                     |                                              | 59,60     |
|              | Mice (adenovirus-mediated gene transfer)    | Increased expression of IL-4, IL-13, eotaxin, and CCR3                                                                               | Induction of AHR by administration of IL-17E | 38        |
| IL-17F       | Bronchial epithelial cells                  | Increased expression of IL-6, IL-8, GRO $\alpha$ , ENA-78, GM-CSF, and ICAM-1                                                        | No effect on CC chemokine expression         | 7,31-33   |
|              | HUVECs                                      | Increased expression of IL-6, IL-8, GRO $\alpha$ , and ENA-78                                                                        |                                              | 31,32     |
|              | Human (asthma)                              | Increased <i>IL17F</i> gene expression in the BALFs                                                                                  |                                              | 7         |
|              | Mice (adenovirus-mediated gene transfer)    | Increased expression of IL-6, IFN- $\gamma$ , IP-10, monokine induced by IFN- $\gamma$ , MCP-1, and MCP-3; induction of neutrophilia |                                              | 38        |
|              | Mice (intratracheal delivery of IL-17F)     | Induction of neutrophilia and CXC chemokines                                                                                         |                                              | 39        |
|              |                                             | Increased AHR and mucus hypersecretion                                                                                               |                                              |           |

AHR, Airway hyperreactivity.

supports this view. To date, the major function of these 3 members is chemoattractant activity through the induction of cytokines and chemokines. Notably, IL-17A and IL-17F share similar functions in terms of their ability to induce chemokines that are important in neutrophil recruitment and activation *in vitro* and *in vivo*, whereas IL-17E is involved in the induction of T<sub>H</sub>2 cytokines and eosinophilic recruitment. Further, several studies have provided evidence for the role of IL-17A and IL-17F in the induction of airway hyperresponsiveness and other pathological changes, including goblet cell metaplasia and airway remodeling. The salient features of the current findings are summarized in Table I and illustrated in Fig 1.

### IL-17A and IL-17F

Since the initial gene discovery of IL-17A and IL-17F, many *in vitro* studies using various target cell types have been pursued, and by far, the most extensively investigated function involves the ability of these 2 cytokines to induce other cytokines, such as IL-6 and GM-CSF, as well

as a panel of chemokines from epithelial and vascular endothelial cells.<sup>26-30</sup> For example, in bronchial epithelial cells, IL-17A is able to induce 2 CXC chemokines: IL-8, growth-related oncogene  $\alpha$  (GRO $\alpha$ ), and epithelial cell-derived neutrophil activating protein 78 (ENA-78). Two additional chemoattractant factors, granulocyte chemotactic protein 2 and monocyte chemoattractant protein (MCP)-1, are also induced in IL-17A-stimulated bronchial epithelial cells *in vitro*. IL-17F has been shown to be able to induce a similar panel of cytokines and chemokines in bronchial epithelial cells and human umbilical vein endothelial cells (HUVECs).<sup>31-33</sup> Besides epithelial and endothelial cells, fibroblasts are known to produce neutrophil-activating factors, IL-6 and IL-8, in response to both IL-17A and IL-17F.<sup>9,29</sup>

Recent efforts with mouse models have corroborated these *in vitro* findings and provided further insight into the functional role of these 2 cytokines *in vivo*. These studies have primarily focused on the regulation of pulmonary responses, involving local (mucosal) administration of

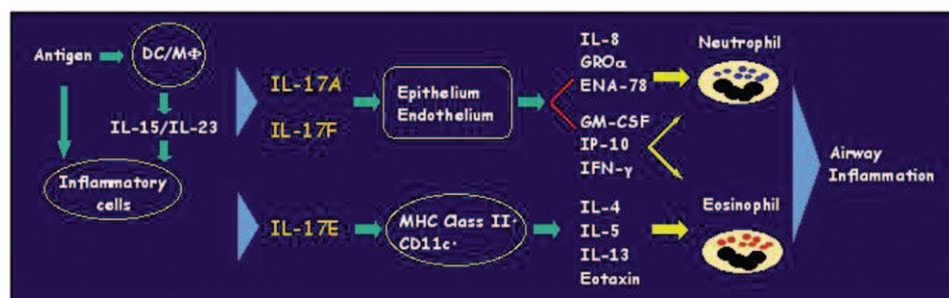


**FIG 1.** Working model for the role of IL-17A, IL-17E, and IL-17F in the expression of airway inflammation. DC, Dendritic cell; MΦ, macrophage.

either recombinant cytokines or gene expression constructs encoding IL-17A or IL-17F. In the first of this series of studies, intratracheal administration of IL-17A significantly increased the absolute number of neutrophils in bronchial alveolar lavage fluids (BALFs).<sup>34</sup> Also, expression of IL-17A via adenovirus-mediated gene transfer resulted in massive peripheral neutrophilia associated with increased level of G-CSF and enhanced granulopoiesis.<sup>35</sup> This effect is specific, because pretreatment of mice with a neutralizing antibody directed against IL-17A significantly reduced pulmonary neutrophilia.<sup>36</sup> Also, in a rat model, IL-17A induces endogenous tachykinins, which in turn, through natural killer 1 receptors, mediate neutrophil recruitment.<sup>37</sup>

Similar approaches for introducing the *IL17F* gene at the mucosal sites have been used, and have led to a similar conclusion. Using an adenoviral gene transfer strategy, overexpression of IL-17F in the mouse airways also leads to an increased number of neutrophils in BALFs.<sup>38</sup> However, using a different model, Oda et al<sup>39</sup> recently provided evidence that overexpression of IL-17F through intratracheal delivery of the IL-17F gene results in an increase in the number of neutrophils and macrophages in the airways. Interestingly, profiling of gene expression for 67 chemokine and 96 cytokine genes showed that genes known to be involved in chemotaxis and activation for monocytes/macrophages and neutrophils, including IL-6, GM-CSF, MCP-1/2, and keratinocyte-derived chemokine (a CXC chemokine), are the most prominently upregulated genes in IL-17F-transduced mouse lungs. In a murine model of asthma, overexpression of IL-17F provided an additive effect on antigen-induced allergic inflammatory responses, characterized, in part, by an increased level of neutrophilia.<sup>39</sup>

In these murine models, eosinophil number was not significantly enhanced in comparison with that seen in mock control mice or mice receiving antigen challenge alone. Also, no effect on the levels of T<sub>H</sub>2 cytokines (IL-4, IL-5, and IL-13) was noted. This selective activity of IL-17A and IL-17F is consistent with the fact that human IL-17F is incapable of inducing CC chemokines, such as eotaxin and RANTES, which are potent chemoattractants for eosinophils, in primary bronchial epithelial cells.<sup>3</sup> To support further the involvement of both cytokines in neutrophil recruitment *in vivo*, a recent study of mice

deficient for IL-23, a potent inducer for IL-17A and IL-17F, shows that those mice are unable to develop neutrophilia in the tissues.<sup>23</sup> Moreover, in our recent unpublished study, an additive effect on the induction of IL-6 and IL-8 has been observed when the cells are treated with IL-17F in combination with either T<sub>H</sub>2 cytokines (IL-4 and IL-13) or T<sub>H</sub>1 cytokine (IFN-γ).

In obstructive airway diseases, including bronchial asthma and chronic obstructive pulmonary disease (COPD), accumulation of neutrophils in the airways has been a major characteristic.<sup>40,41</sup> Neutrophil recruitment into the airways is regulated through the chemokine network, and bronchial epithelial cells and vascular endothelial cells are important cellular sources of CXC chemokines. Increased expression of the 3 CXC chemokines IL-8, GROα, and ENA-78 has been found in various human diseases, including acute respiratory distress syndrome and bacterial pneumonia, in which abundant neutrophils are a major feature.<sup>42</sup> The potent stimulatory activity of both IL-17A and IL-17F on the expression of cytokines and chemokines suggests their intimate associations with the recruitment and activation of neutrophils and potential contribution to the pathogenesis of these diseases. Further, the induction of GM-CSF from epithelial cells by IL-17A and IL-17F is noteworthy, because among its pleiotropic functions, GM-CSF has multiple effects on neutrophil effector functions, including the induction of 5-lipoxygenase, superoxide generation, degranulation, and cytotoxicity.<sup>43</sup>

### Involvement of IL-17A and IL-17F in pulmonary allergic responses

Allergic asthma is characterized by a local T<sub>H</sub>2-biased immune response; changes of remodeling, including epithelial hypertrophy; subepithelial fibrosis; goblet cell hyperplasia/metaplasia; and airway hyperreactivity (see review<sup>44</sup>). One of the most prominent features of airway remodeling is subepithelial fibrosis, which serves as a potential marker for disease severity.<sup>45</sup> Current studies have provided evidence for the involvement of IL-17A and IL-17F in these pathological processes. It has been reported that IL-17A is able to induce the expression of 2 mucin genes, *MUC5AC* and *MUC5B*, in bronchial epithelial cells,<sup>46</sup> and that an increased expression of IL-17A is associated with enhanced mucin gene expres-

sion *in vivo*.<sup>47</sup> In a recent study of a mouse model, overexpression of IL-17F also resulted in goblet cell hyperplasia and mucin gene expression, but only when the mice were challenged with antigen, and increased goblet cell hyperplasia was seen only in the small airways.<sup>39</sup> Although it is unclear currently whether IL-17F has a direct effect on the expression of mucin genes, these results suggest that in addition to IL-13, both IL-17A and IL-17F may be important contributors to pulmonary mucus hypersecretion.

In addition to their role in the induction of CXC chemokines, IL-17A and IL-17F have been shown to induce several profibrotic cytokines. For example, in fibroblasts isolated from bronchial biopsy of subjects with asthma, IL-17A enhances the production of 2 profibrotic cytokines, IL-6 and IL-11,<sup>48</sup> and IL-17F has been shown to be able to induce the expression of TGF- $\beta$  in human umbilical vein endothelial cells (HUVECs<sup>8</sup>). TGF- $\beta$  is a profibrotic cytokine and has been implicated in the extracellular matrix changes observed in fibrosis. IL-11 is produced by many cell types, including human lung fibroblasts and alveolar and airway epithelial cells, and is involved in subepithelial fibrosis.<sup>49</sup> In addition, increased expression of both TGF- $\beta$  and IL-11 was found in the airways of patients with asthma and correlated with disease severity.<sup>18</sup> Although direct proof is needed, the *in vitro* activity of IL-17A and IL-17F in inducing profibrotic cytokines and increased expression of IL-17A, IL-11, and TGF- $\beta$  in subjects with asthma<sup>18</sup> suggest their potential role in airway remodeling.

In addition to those mucosal responses, a recent study of IL-17A-deficient mice showed that IL-17A is involved in the activation of allergen-specific T cells. In those mice, decreased levels of IL-4 and IL-5, but not IFN- $\gamma$ , were seen,<sup>50</sup> which are associated with reduced level of airway hypersensitivity. In addition, a decreased level of IgE was seen in this model.<sup>50</sup> It appears, therefore, that IL-17A not only is involved in the regulation of tissue mucosal response but also has a systemic effect on the development of the T<sub>H</sub>2 cell response. The regulatory mechanisms for this interesting observation remain to be explored.

In human beings, studies of IL-17A and IL-17F expression in patients with asthma have been pursued. In patients with asthma, IL-17A is significantly expressed,<sup>18,48</sup> and its level in sputum of patients with asthma correlated negatively with PC<sub>20</sub> to methacholine.<sup>51</sup> Also, analyses of gene expression in BALF cells from subjects with asthma challenged with allergen or saline control showed enhanced IL-17F gene expression at allergen-challenged sites of study subjects.<sup>7</sup>

### Involvement of IL-17A in antimicrobial activity

Although the exact role of the IL-17 cytokine family in host defense against infection remains to be defined, current data primarily on the basis of *in vitro* studies have suggested its involvement in the host defense mechanisms. For example, in a recent study<sup>52</sup> screening a panel of 21 cytokines, IL-17A was the most potent stimulatory cytokine inducing the expression of human  $\beta$ -defensin-2

(hBD-2) and macrophage inflammatory protein 3 (MIP-3). Both  $\beta$ -defensin-2 and MIP-3 are essential components of airway innate immunity.<sup>53,54</sup> The known function of hBD-2 in innate immunity is believed to be related to its antimicrobial activity and to its chemotactic effects on immature dendritic cells and memory T cells.<sup>53</sup> Thus, the stimulatory effects of IL-17A on hBD-2 and MIP-3 expression, in conjunction with its activity in neutrophil recruitment and activation, suggest an important role of IL-17A in host defense from the innate response to adaptive immune mechanisms. It is noted that mice lacking the receptor for IL-17A, IL-17R, are unable to develop full neutrophil response to *Klebsiella pneumoniae* infection in the airways.<sup>55</sup> Also, overexpression of IL-17A in the lungs using a recombinant adenovirus encoding mouse IL-17A (AdIL-17) resulted in enhanced bacterial clearance and survival after challenge with *K pneumoniae*.<sup>56</sup>

Taken together, current evidence suggests that IL-17A and IL-17F are involved in the regulation of pulmonary inflammation at multiple levels, in part through the induction of other cytokines and chemokines. These responses provide important defense mechanisms against infectious pathogens, and functional defects in these responses would increase the susceptibility to specific pathogens. In contrast, exaggerated production of IL-17A and IL-17F may contribute to the expression of airway inflammation and pulmonary hyperreactivity. Moreover, IL-17A has been shown to be able to induce the activity of inducible nitric oxide synthase and nitric oxide production in both mouse and rat endothelial cells.<sup>57</sup> Further, analysis of lung tissues from IL-17F gene-transduced mice<sup>38</sup> showed substantial increases in the levels of IFN- $\gamma$  and IFN- $\gamma$  inducible protein 10 (IP-10; a CXC chemokine contributing to the expression of pulmonary allergic responses<sup>58</sup>). These additional functional activities of IL-17A and IL-17F may thus further amplify the inflammatory responses.

Although a comprehensive and comparative analysis of IL-17F and IL-17A has not yet been pursued, IL-17F appears to have biological actions similar to those of IL-17A. So far, the only functional difference reported is the ability of IL-17F (the shorter form) to induce intracellular adhesion molecule 1 (ICAM-1<sup>7</sup>), whereas the induction of ICAM-1 by IL-17A occurs only when IFN- $\gamma$  is present in the culture.<sup>27</sup> Further, indirect evidence has suggested that IL-17F may use a different receptor.<sup>7</sup> This suggests an incomplete redundancy for these 2 closely related cytokines, but further in-depth comparative studies are required to define the redundant and the distinct function of these 2 cytokines.

### Unique function of IL-17E

In comparison with the functions of IL-17A and IL-17F, another member of this family, IL-17E, induces a different set of cytokine genes and is involved in T<sub>H</sub>2-type immune response and pathological changes. Transgenic overexpression of IL-17E results in airway eosinophilia and an increase in serum levels of IL-5, IL-13, and IgE.<sup>59,60</sup> Elevated levels of gene expression for several T<sub>H</sub>2

cytokines, including IL-4, IL-5, IL-10, and IL-13, were observed in multiple tissues. Also, intranasal administration of IL-17E-expressing adenovirus vector results in the production of IL-4, IL-5, IL-13, and eotaxin, and eosinophilia in lung tissue and BALF.<sup>38</sup> In addition, epithelial cell hyperplasia, increased mucus secretion, and airway hyperreactivity are developed in mice on intraperitoneal administration of recombinant IL-17E.<sup>38</sup> Interestingly, when the induction of T<sub>H</sub>2 cytokines was analyzed *in vitro*, the major cell type in response to IL-17E appears to be a non-T/non-B cell population expressing class II MHC and CD11c molecules, a typical accessory cell phenotype.<sup>19</sup> These findings suggest that IL-17E is a unique member of the IL-17 cytokine family and is directly involved in T<sub>H</sub>2-associated allergic inflammation.

### WORKING MODEL FOR THE ROLE OF IL-17A, IL-17E, AND IL-17F IN THE EXPRESSION OF AIRWAY INFLAMMATION

On the basis of currently available data, it can be envisaged that all 3 members of the IL-17 cytokine family are produced from activated inflammatory cells, including T cells and mast cells (a cell type producing IL-17F and IL-17E), which leads to subsequent recruitment and activation of leukocytes. Although both IL-17A and IL-17F selectively induce endothelial and/or epithelial cell-derived CXC chemokines, such as IL-8, GRO $\alpha$ , and ENA-78 for neutrophil influx, IL-17E preferentially induces T<sub>H</sub>2 cytokines and eotaxin for eosinophil recruitment. These, together with other inflammatory changes including mucous hypersecretion associated with increased activities of the 3 cytokines, lead ultimately to pulmonary inflammation and tissue injury. The additive effect of IL-17F with either T<sub>H</sub>2 cytokines (IL-4 and IL-13) or T<sub>H</sub>1 cytokine (IFN- $\gamma$ ) may further amplify leukocyte infiltration and allergic inflammation. Moreover, the induction of IL-17A and IL-17F through dendritic cell/macrophage-derived IL-15 and IL-23 would confer an antimicrobial activity in conjunction with subsequent recruitment/activation of neutrophils and nitric oxide production. IL-17A and IL-17F may also facilitate influx of other inflammatory cells, including eosinophils, and amplify pulmonary inflammatory response through the induction of other cytokines and chemokines, such as GM-CSF, IFN- $\gamma$ , and IP-10 (Fig 1).

### RECEPTORS AND ASSOCIATED SIGNALING PATHWAYS

To date, only the receptors for IL-17A and IL-17E have been characterized. The receptor for IL-17A, IL-17R,<sup>61</sup> was initially discovered in mice by the use of a viral homologue of IL-17A as a ligand, which was found to be able to bind to both human and mouse IL-17A.<sup>2,61</sup> Compared with other known cytokine receptor families,

the structure of IL-17R, a type 1 membrane receptor, is quite unique. The cytoplasmic domain of IL-17R lacks conserved signaling domains commonly seen in other cytokine receptors. The IL-17R gene is constitutively expressed in several human cell types, such as a lung epithelial cell line, foreskin fibroblasts, a B-cell line, a myelomonocytic cell line, and an embryonal kidney cell line.<sup>2</sup> The human IL-17A receptor exhibits 69% sequence homology with the mouse counterpart, and direct binding assays of IL-17R-transfected cells and labeled human IL-17A have revealed a relatively low-affinity binding with an association constant value ranging between 10<sup>7</sup> and 10<sup>8</sup> M.<sup>61</sup> This low-affinity binding suggests the existence of an additional binding subunit to form a high-affinity binding complex, because relatively low concentrations (nanogram range) of IL-17A are sufficient to exert its biological activity, but its existence and identity remain a subject of investigation.

Studies of the other members of the IL-17 family also suggest the existence of distinct receptors. IL-17E has been identified as a high-affinity ligand for a newly recognized receptor.<sup>3,6</sup> This receptor has also been demonstrated to interact with IL-17B with low affinity.<sup>6</sup> Sequence comparison of the receptors for IL-17A and IL-17E reveals similar overall structure with conservation of several cysteines within the extracellular domains, and also with conserved elements within the intracellular domain, suggesting that these receptors likely engage similar signaling pathways. Indeed, both IL-17A and IL-17E are able to induce the activation of nuclear factor  $\kappa$ B (NF $\kappa$ B) and a similar, but not identical, panel of cytokines and chemokines.

To date, the receptor for IL-17F has not been identified, but indirect evidence suggests a distinct cognate receptor. For example, by using the shorter form of IL-17F, Kawaguchi et al<sup>7</sup> performed competitive inhibition experiments to assess whether it interacts with the receptor for IL-17A by measuring the level of IL-17F-induced ICAM-1 gene expression in the presence of varying concentrations of the competitor, IL-17A. The level of IL-17F-induced ICAM-1 expression was not inhibited by the inclusion of IL-17A in the culture, even at a 20-fold higher concentration (2000 ng/mL). Further work is needed to uncover the signaling pathways, including the nature of the putative IL-17 receptor. Four additional IL-17R-related receptors have been identified through sequence homology searches, but the nature of their respective ligands remains elusive.

Although the identity of the receptors for several of the IL-17 family members is still unclear, recent studies of the signaling events associated with IL-17A-induced and IL-17F-induced cellular activation and cytokine expression have been informative. IL-17A is known to activate all 3 subgroups of mitogen-activated protein kinases, the extracellular signal-regulated kinases (ERK1 and ERK2), Jun NH2-terminal kinases, and p38 in several cell types, including bronchial epithelial cells.<sup>26,27</sup> Activation of p38 mitogen-activated protein kinase by IL-17A results in up-regulation of inducible nitric oxide synthase and COX-2

genes.<sup>57</sup> In a monocytic leukemia cell line, U937, IL-17A triggers tyrosine phosphorylation of several members of the Janus kinase family, 1, 2, and 3, and signal transducer and activator of transcription 1, 2, 3, and 4.<sup>62</sup> In the downstream signaling pathway, IL-17A activates transcription factor NF $\kappa$ B, which depends on TNF receptor-associated factor 6, but not TNF receptor-associated factor 2.<sup>63</sup> In addition to IL-17A, IL-17D and IL-17E are able to activate NF $\kappa$ B.<sup>5,6,26</sup>

In primary bronchial epithelial cells and endothelial cells, IL-17F induces the activation of ERK1/2.<sup>31-33</sup> In contrast, no activation of p38 and Jun NH2-terminal kinase kinases was seen at any time point, even after 4-hour stimulation of the cells with IL-17F, despite the high sequence homology between IL-17A and IL-17F. These results suggest, therefore, that the members of the IL-17 cytokine family are capable of activating similar, but not identical, intracellular signaling pathways. It is noted, however, that induction of both IL-6 and IL-8 is not completely inhibited by ERK kinase inhibitors, suggesting that additional signaling pathways are involved in these cytokines induced by IL-17F in these cell types.

## CONCLUSION

Taken together, current data from structural and functional analyses have defined a new cytokine family and suggested that this family of cytokines is capable of eliciting profound immunological effects and is, therefore, likely to play an important role in immunoregulation. The diverse tissue expression patterns and pleiotrophic functions of the IL-17 cytokine family with a distinct ligand-receptor signaling system may thus generate a new paradigm within the cytokine network contributing to the maintenance of homeostasis and the expression of inflammatory diseases. Increased understanding of the complexity of the cytokine network, together with characterization of relevant novel genes, would help to uncover the molecular mechanisms of inflammatory diseases. Indeed, members of the IL-17 cytokine family are associated with inflammatory diseases and are able to induce a wide range of cytokines and chemokines that are crucial in the regulation of inflammatory response. Specifically, through memory T-cell responses, IL-17A and IL-17F are able to promote the recruitment of monocytes and neutrophils via the induction of chemokines. This activity, together with the involvement of IL-17A (and likely IL-17F) in the development of the T<sub>H</sub>2 responses and with the participation of IL-17E in the expression of T<sub>H</sub>2 cytokines, may thus potentiate and amplify allergic inflammation. Further detailed investigation with emphasis on defining the regulatory mechanisms of its expression, the ligand-receptor signaling pathways, and the pathways leading to the concerted effect with other cytokines would be important in defining the molecular basis of this cytokine family's involvement in immunoregulation.

## Therapeutic implications

Current data support the notion that IL-17A and IL-17F are involved in host defense against bacterial infection. The use of recombinant proteins (and the derivatives thereof) and/or the strategy for correcting the deficiency of both cytokines would have a prophylactic and therapeutic potential.

The finding that exaggerated response of both IL-17A and IL-17F results in neutrophilic inflammation offers an experimental basis for developing strategies to antagonize the dysregulated cytokine response in diseases such as asthma and COPD in which neutrophilic inflammation is important in lung injury.

Upregulated IL-17E activity is associated with systemic and localized T<sub>H</sub>2 responses, offering an attractive therapeutic target for modulation in T<sub>H</sub>2-associated allergic diseases.

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