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Interleukin-17 Family Members and Inflammation

Review

Jay K. Kolls[1,]* and Anders Lindén[2]
[1]Division of Pulmonology
Department of Pediatrics
Children's Hospital of Pittsburgh and
the University of Pittsburgh
Pittsburgh, Philadelphia
[2]Department of Allergology & Respiratory Medicine
Institute of Internal Medicine
The Sahlgrenska Academy at the University of Göteborg
S-413 45 Göteborg
Sweden

IL-17A was cloned more than 10 years ago and six IL-17 family members (IL-17A-F) have subsequently been described. IL-17A is largely produced by activated memory T lymphocytes but stimulates innate immunity and host defense. IL-17A and IL-17F both mobilize neutrophils partly through granulopoeisis and CXC chemokine induction, as well as increased survival locally. IL-17A and IL-17F production by T lymphocytes is regulated by IL-23 independent of T cell receptor activation. Increasing evidence shows that IL-17 family members play an active role in inflammatory diseases, autoimmune diseases, and cancer. This places IL-17 family members and their receptors as potential targets for future pharmacotherapy.

IL-17A and the IL-17 Family

Interleukin (IL)-17A was originally described and cloned by Rouvier et al. (1993) and named CTLA8, was subsequently renamed IL-17, and more recently, IL-17A. The gene location for IL-17A is 6p12 (Moseley et al., 2003) (Table 1), and IL-17A shows 58% homology with an open reading frame of the T lymphotropic herpesvirus samirii (viral IL-17). IL-17A is the prototypic IL-17 family member (Table 1) in that it is a disulfide-linked homodimeric glycoprotein consisting of 155 amino acids (Yao et al., 1995), exerting its actions as a homodimer with a molecular weight around 35 kDa. Mouse and rat IL-17A displays significant structural homology with human IL-17A (Table 1), both having remarkably conserved glycosylation sites (Moseley et al., 2003). Homology-based cloning has recently revealed five additional IL-17 family members (Table 1), termed IL-17B to IL-17F (Li et al., 2000; Starnes et al., 2001; Hurst et al., 2002; Lee et al., 2001; Fort et al., 2001). These molecules also form homodimers and show conservation in their c-terminal region, with five spatially conserved cysteine residues accounting for a characteristic cysteine-knot formation for IL-17A and IL-17F (Hymowitz et al., 2001). Among the IL-17 family members, the IL-17F isoforms 1 and 2 (ML-1) have the highest degree of homology with IL-17A (55 and 40% respectively), followed by IL-17B (29%), IL-17D (25%), IL-17C (23%), and IL-17E (also named IL-25) being most distant (17%) (Figure 1).

*Correspondence: jay.kolls@chp.edu

Cellular Sources of the IL-17 Family Members

IL-17A was initially described at the message level as a product of activated $CD4^+$ memory T lymphocytes from peripheral blood (Yao et al., 1995; Fossiez et al., 1996). However, data in mice (Happel et al., 2003; Ferretti et al., 2003) and humans (Shin et al., 1999) have subsequently demonstrated that $CD8^+$ memory T lymphocytes can also produce IL-17A after stimulation, more specifically the $CD45RO^+$ subset. Interestingly, IL-17F resides just 46,050 base pairs away from IL-17A on chromosome 6 in humans and on chromosome 1 in mice and, given their similar expression profile in activated T lymphocytes, suggest that regulatory regions exist within the IL-17A/F locus, controlling their expression. IL-17A expression does not segregate to $CD4^+$ T-lymphocytes with a Th1 or Th2 profile (Infante-Duarte et al., 2000). In response to stimulation by lipopetides from *Borrelia burgdorferi*, IL-17A localizes to a subset of T lymphocytes expressing tumor necrosis factor (TNF)-α and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Infante-Duarte et al., 2000). In support of subsets of T lymphocytes being a major source for IL-17A in host defense, mice which lack T lymphocytes (SCID) or mice depleted of $CD4^+$ and $CD8^+$ T lymphocytes (using antibodies) have over a 90% reduction in IL-17A concentration within the lung after endotoxin exposure (Ferretti et al., 2003) (Happel et al., 2003). In addition to T lymphocytes, IL-17A message or intracellular protein has been detected in eosinophils and neutrophils and human blood monocytes but release of free, soluble IL-17A protein has not been reported (Molet et al., 2001; Ferretti et al., 2003). (Awane et al., 1999).

IL-17B was cloned by using a homology-based EST database search followed by amplification from a fetal tissue cDNA library and is expressed as a noncovalent dimer (Li et al., 2000; Shi et al., 2000). It is expressed in the pancreas, small intestine, stomach, and in the spinal cord as well (Li et al., 2000; Moore et al., 2002). IL-17C, on the other hand, has a different expression profile, being detected in human testes, thymus, spleen, and prostate (Moseley et al., 2003). IL-17D was cloned by homology and RACE-PCR and is expressed in skeletal muscle, neuronal cells, the prostate, and lesser amounts in resting $CD4^+$ T lymphocytes (Starnes et al., 2002). In contrast to IL-17A and IL-17F, IL-17D is not induced in activated B- or T lymphocytes (Starnes et al., 2002). The most divergent known member of the IL-17 family is IL-17E (IL-25) (Figure 1, Table 1); it is expressed in the brain, lung, testis, and prostate at low levels in human tissues (Lee et al., 2001) and in mouse T lymphocytes of the $CD4^+$ subset with a Th2 profile (Fort et al., 2001).

Proximal Regulators of IL-17 Family Members In Vitro and In Vivo

IL-17A and IL-17F may now be regarded as molecules mediating the stimulation of neutrophil mobilization by T lymphocytes (see the section titled "IL-17 Signaling and Tissue Inflammation" below for further details). This unique position, at the interface between adaptive and

Table 1. Overview of the Human IL-17 Family of Cytokines

IL-17 Subtype	Size (kDA)	Length (Number of aa)	Chromosomal Location	Homology of Murine to Human
A	35	155	6p12	62
B	41	180	5q32-34	88
C	40	197	16q24	83
D	52	202	13q12.11	78
E	34	161	14q11.2	81
F	44	153	6p12	77

All cytokines in this table are homodimeric glycoproteins incorporating cysteine residues and disulphide linkages (except IL-17B).

innate immunity, has potential implications not only for host defense but also for specific inflammatory diseases. Recently, major research efforts have focused on defining upstream regulators of IL-17 family members. Two cytokines, IL-15 and IL-23, have been shown to regulate the release of the T lymphocyte-expressed IL-17 family members. IL-15 induces IL-17A production in $CD4^+$, but not $CD8^+$, T lymphocytes from mice (Ferretti et al., 2003). This action of IL-15 has also been confirmed in human blood mononuclear cells cultured in vitro (Ziolkowska et al., 2000). The role of IL-15 in regulating IL-17A and IL-17F in vivo has yet to be determined but, as IL-15 is critical for the maintenance of T lymphocytes of the memory subset, the IL-15–IL-17 axis may be critical in chronic inflammation.

Compared with the case for IL-15, an even stronger case can be made for IL-23 as a proximal regulator of IL-17A and IL-17F. IL-23 is a heterodimer, consisting of the unique IL-23 p19 subunit and the p40 subunit it shares with IL-12 (Oppmann et al., 2000). This proximal regulator signals through the IL-12β1 and IL-23 receptor, and it potently induces IL-17A and IL-17F in human and mouse T lymphocytes. IL-23 specifically stimulates memory ($CD44^{high}/CD62L^{low}$) $CD4^+$ T-lymphocytes to produce IL-17A, although mouse $CD8^+$ T-lymphocytes also respond to IL-23 in vitro (Aggarwal et al., 2003; Happel et al., 2003). Importantly, T lymphocytes stimulated with either endotoxin or heat-killed, gram-negative bacteria do not produce IL-17A, unless dendritic cells are present (Happel et al., 2003). The IL-17A response by T lymphocytes is dependent upon dendritic cells producing IL-23 through a Toll-like receptor 4-dependent pathway (Happel et al., 2003). Thus, IL-23 induces the production of IL-17A in T lymphocytes, without requiring classical physical cell-to-cell contact between these cells and dendritic cells in vitro (Happel et al., 2003). Inhibiting IL-15 does not affect this IL-17A production and, thus, IL-15 is not required for the induction of IL-17A by gram-negative bacteria. Taken together, it is likely that both IL-17A and IL-17F are regulated by IL-23 in vivo. In contrast, IL-12 p70 signaling via IL-12Rβ2 decreases IL-17A release from mouse splenocytes in vitro (Aggarwal et al., 2003). This differential regulation of IL-17 by IL-23 and IL-12 has recently been shown to occur in vivo as well in the setting of autoimmune arthritis, as IL-12 p35-deficient mice have a higher frequency of IL-17A-producing T cells and exacerbated inflammation (Murphy et al., 2003). Thus, several members of the IL-12 family of cytokines, including IL-27, may regulate IL-17 responses. Since IL-12 largely signals through STAT4 and IL-23 induces STAT3/4 heterodimers (Trinchieri et al., 2003), the regulation of IL-17 family members by IL-12 family members deserves further characterization (Figure 2).

Receptors for IL-17 Family Members

The originally described IL-17 receptor (IL-17R) (Yao et al., 1995) (Table 2) is a type I transmembrane protein consisting of a 293 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a long 525 amino acid cytoplasmic tail (Yao et al., 1995). Its mRNA is extensively expressed in the lungs, kidneys, liver, and spleen as well as in isolated fibroblasts, epithelial cells, mesothelial cells, and various myeloid cells from rats and mice (Yao et al., 1995). Among human cells, the messenger RNA for IL-17R can be detected in epithelial cells, fibroblasts, B and T lymphocytes, myelomonocytic cells, and marrow stromal cells (Silva et al., 2003). The IL-17R protein itself can be detected in peripheral blood T lymphocytes and in vascular endothelial cells from humans (Moseley et al., 2003). Remarkably, the human IL-17R binds IL-17A with a relatively low affinity and at a potency that is approximately 10-fold weaker than the cytokine response (IL-6 release) to IL-17A, arguing that there may be additional receptors involved in IL-17A-induced cell signaling (Yao et al., 1995). However, evidence does not support an additional high-affinity subunit receptor, as mice with a homozygous deletion of IL-17R have no detectable binding of IL-17A in B- or T lymphocytes (Ye et al., 2001b). Moreover, homozygous deletion of IL-17R abrogates the increase in splenic neutrophil progenitors resulting from the overexpression of IL-17A (Ye et al., 2001b). Because IL-17F has a high degree of homology with IL-17A and has a similar spectrum of activity in terms of induction of G-CSF and CXCL8 (Hurst et al., 2002), IL-17F may use IL-17R for signaling; however, neither binding nor competition experiments have supported this (Hymowitz et al., 2001).

Five additional IL-17 receptors have now been described; these are IL-17RB-E (Table 2). Similar to IL-17 R, they are type I transmembrane proteins but display significant alternative splicing (Moseley et al., 2003). IL-17RB (aka Evi27) is expressed in human kidney, pan-

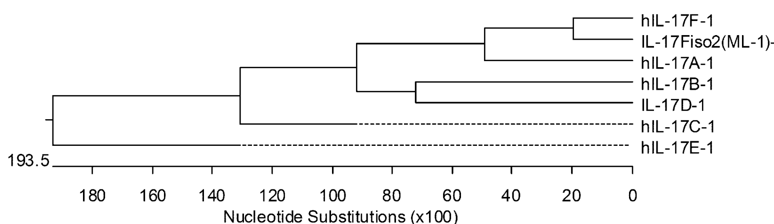

Figure 1. Dendogram Analysis of IL-17 Family Members

Protein sequences of IL-17 family members were aligned and phylogenetically characterized by using the Clustal W method in Megalign (DNASTAR).

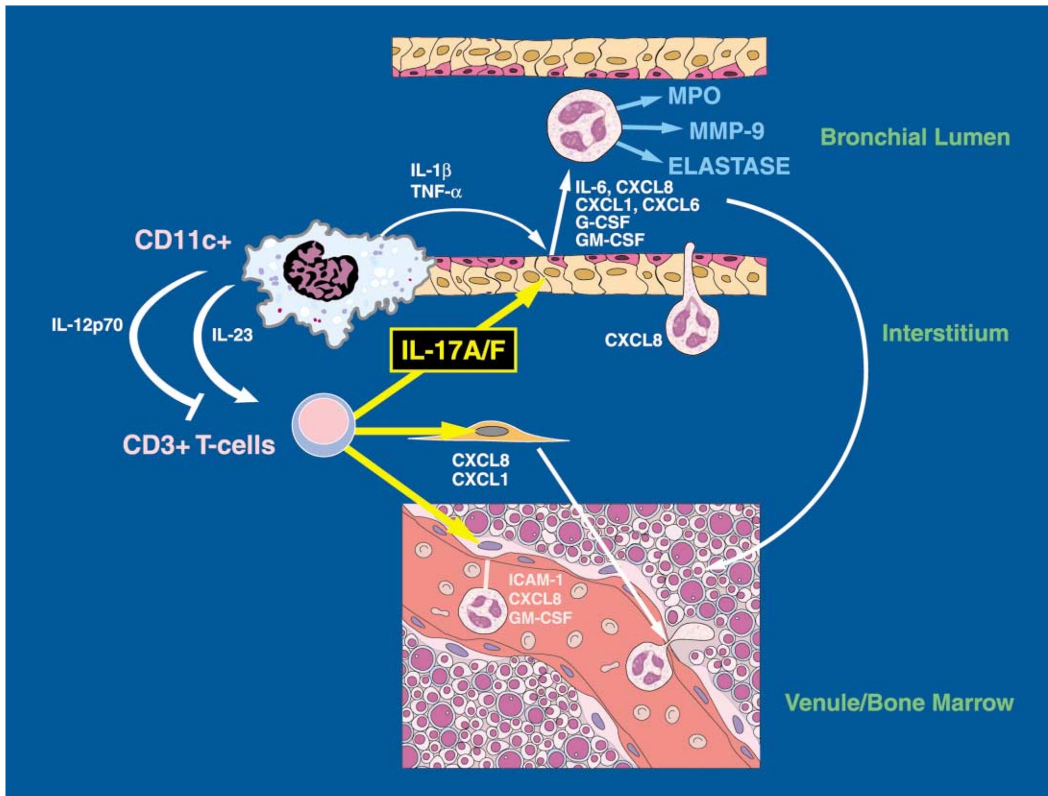

Figure 2. Hypothesized IL-17 Signaling in Airway Inflammation

Mucosal T-lymphocytes can produce IL-17A/F in response to proximal triggers such as IL-23 from macrophages or dendritic cells or IL-15, and IL-17A/F can signal via receptors expressed on epithelial cells, fibroblast, and endothelial cells. IL-17A/F subsequently induces chemokines (CXCL8, CXCL6, CXCL1), growth factors (G-CSF, GM-CSF, IL-6), and adhesion molecules (ICAM-1), leading to augmented neutrophil accumulation as well as to granulopoeisis. IL-12p70 can inhibit IL-17 A/F elaboration by T cells.

creas, liver, brain, and intestines and serves as a receptor for IL-17B as well as for IL-17E with IL-17E binding more avidly than IL-17B (Shi et al., 2000; Lee et al., 2001). IL-17RC is expressed in human prostate, cartilage, kidney, liver, heart, and muscle (Haudenschild et al., 2002; Moseley et al., 2003). Interestingly, this receptor undergoes alternative splicing with some forms being secreted but potentially maintaining ligand binding capabilities, and thus these isoforms may potentially inhibit IL-17 receptor family members from ligand-induced signaling (Haudenschild et al., 2002). IL-17RD also exhibits alternative splicing as well (Moseley et al., 2003), and one such product may inhibit fibroblast growth factor (FGF)-induced receptor tyrosine kinase activity (Yang et al., 2003). Finally, IL-17RE is expressed in human brain, prostate, and pancreas, but its ligand preferences remain to be described in detail (Clark et al., 2003).

IL-17 Signaling and Tissue Inflammation

Most experimental evidence to date suggests a role for IL-17 family members in coordinating local tissue inflammation mainly via the induced release of proinflammatory and neutrophil-mobilizing cytokines (Figure 2).

Studies in Vitro

C-X-C Chemokines. Stimulation with recombinant IL-17A (rIL-17A) protein causes the production and release of CXCL8 (IL-8) in human bronchial epithelial and venous endothelial cells, as well as in human synoviocytes obtained from rheumatoid synovium (Laan et al., 1999;

Table 2. Overview of the Human IL-17 Receptor Family

IL-17 R Subtype	Ligand Specificity	Length (Number of aa)	Chromosomal Location	Homology of Murine to Human (%)
IL-17R	IL-17A/?IL-17F	866	22q11.1	68
IL-17RB (IL-17RH1)	IL-17B/IL-17E	499*	3p21.1	82
IL-17RC (IL-17RL)	unknown	791*	3p25.3	71
IL-17RD(hSEF)	?ligand for FGF-R	595*	3p21.2	90
IL-17RE	unknown	667*	3p25.3	82

*Alternatively spliced isoforms exist.

Fossiez et al., 1996; Laan et al., 2001; Kawaguchi et al., 2001a; Prause et al., 2003; Jones and Chan, 2002). This is of interest since these cell types represent critical barriers for neutrophil invasion. CXCL8 accounts for a significant component of IL-17A- induced chemotactic activity, as a neutralizing anti-CXCL8 antibody significantly attenuates the human neutrophil chemotactic activity of conditioned media obtained from IL-17A stimulated bronchial epithelial cells (Laan et al., 1999). Moreover, CXCL8 release is specific for IL-17A protein as well, as pretreatment of rIL-17A with a specific neutralizing antibody attenuates its effect. Similarly, IL-17F stimulates CXCL8 in fibroblasts (Hymowitz et al., 2001), and IL-17D can induce CXCL8 in endothelial cells, possibly through nuclear translocation of NF-κB (Starnes et al., 2002). IL-17E also activates nuclear factor-kappa B (NF-κB) through IL-17BR and results in CXCL8 induction in kidney cells (Lee et al., 2001). Stimulation with IL-17A or IL-17F also releases CXCL1 (growth related oncogene (GRO)-α) and granulocyte chemotactic protein (GCP)-2 in human bronchial epithelial and mesothelial in vitro (Prause et al., 2003; Jones and Chan, 2002; Witowski et al., 2000). The induced gene expression and protein release for CXCL8 and CXCL1 induced by IL-17A is comparable with that caused by the proinflammatory cytokine TNF-α (Jones and Chan, 2002). It is not yet confirmed whether stimulation with IL-17A or IL-17F induces the release of CXCL8 and other C-X-C chemokines via a NF-κB-inducing kinase in resident lung cells, as is the case for CXCL8 in response to proinflammatory stimuli other than IL-17A (Mori et al., 1999; Harper et al., 2001; Kennedy et al., 1998). However, in human synoviocytes in vitro IL-17A induction of CXCL8 depends upon NF-κB and the PI-3 kinase/Akt pathway (Hwang et al., 2004).

Mitogen-activated protein (MAP) kinases, in particular p38 and extracellular signal-regulated kinase (ERK), are involved as mediators of IL-17A-induced release of C-X-C chemokines in human bronchial epithelial cells in vitro (Laan et al., 2001; Kawaguchi et al., 2001a; Prause et al., 2003). In IL-17A-induced bronchial epithelial cells, the release of CXCL8, CXCL1, and CXCL6 release, and the CXCL8 release in primary human bronchial smooth muscle cells is relatively insensitive to glucocortocoid inhibition (Vanaudenaerde et al., 2003; Prause et al., 2003; Jones and Chan, 2002). In contrast, primary human lung fibroblasts, optimally located to communicate with the neutrophil after extravasation into lung tissue, produce CXCL8 in response to IL-17A, and these responses are sensitive to glucocorticoid inhibition in vitro (Molet et al., 2001). Taken together, these data suggest that IL-17A signaling differs among resident lung cells.

Similar to the case in human bronchial epithelial cells, IL-17A induces an increase in the mRNA for another C-X-C chemokine, CINC, in rat intestinal epithelial cells in vitro (Awane et al., 1999). The activation of the CINC mRNA promoter involves TNF receptor-associated factor-6 (TRAF6) (Awane et al., 1999). This mRNA expression is also dependent upon a NF-κB-inducing kinase (NIK), as well as IκB kinase (IKK)-α. Furthermore, the expression of CINC mRNA involves MAP kinases, including ERK and p38, as well as the Ras pathway. Lastly, IL-17A was also shown to inhibit cellular proliferation of rat intestinal epithelial cells as well (Awane et al., 1999).

IL-6 and Mucins. Tissue fibroblasts and human bronchial epithelial cells respond to IL-17A by releasing the potentially neutrophil-activating cytokine IL-6 in vitro, and this activity has been used as a bioassay for IL-17A (Yao et al., 1995) (Kawaguchi et al., 2001a; Molet et al., 2001). Similar to CXCL8, the involvement of the MAP kinase ERK has been confirmed (Laan et al., 1999; Kawaguchi et al., 2001a). However, it is not known whether this response is sensitive to glucocortocoids. Among all the interleukins from IL-1 to IL-18, only IL-6 and IL-17A can increase mRNA and protein for the mucins MUC5AC and MUC5B, at least in primary human bronchial epithelial cells in vitro (Chen et al., 2003). For IL-17A, this effect, in part, is mediated by IL-17-induced IL-6, which subsequently results in an increase in mucin protein in these cells. Interestingly, IL-17B, IL-17C, and IL-17F also induce IL-6 in human fibroblasts, whereas IL-17D induces IL-6 in human venous endothelial cells in vitro (Li et al., 2000; Starnes et al., 2002; Awane et al., 1999).

MCP-1. Stimulation with IL-17A also induces an increase in the messenger RNA for the C-C chemokine monocyte chemotactic protein (MCP)-1 in rat intestinal epithelial cells in vitro (Awane et al., 1999). Even though this finding may have interesting implications for the accumulation of monocyte-lineage cells in the tissue of several organs, its functional importance remains to be characterized.

TNF-α and IL-1β. Certain monocytic cells respond to IL-17A by releasing proinflammatory cytokines when cultured in vitro. For example, isolated human blood monocytes release TNF-α and IL-1β when stimulated with rIL-17A in vitro (Jovanovic et al., 1998). Noteworthy, however, alveolar and peritoneal macrophages from mice lack IL-17R expression and fail to secrete TNF-α, as well as CXCL2 and IL-6 in response to IL-17A (Kolls et al., 2003). Moreover, studies in the human monocytic cell line, THP-1, IL-17B and IL-17C, but not IL-17A, induce TNF-α and IL-1β (Li et al., 2000). It therefore remains unknown what human macrophage populations can directly respond to the various IL-17 family members; however, data strongly support a role for IL-17B and C in monocyte TNF-α and IL-1β production.

Colony-Stimulating Factors. IL-17A and IL-17D can induce the production and/or release of at least two different colony-stimulating factors in vitro. This includes granulocyte colony-stimulating factor (G-CSF) in venous endothelial cells and fibroblasts as well as GM-CSF in bronchial epithelial cells from humans (Jones and Chan, 2002; Starnes et al., 2002). The effect of IL-17A on GM-CSF is regulated by glucocortocoids and is probably a functionally significant one, as judged from its impact on survival of isolated human blood neutrophils cultured in vitro (Laan et al., 2003). IL-17A increases G-CSF by both increasing its transcription and by stabilizing its mRNA in mouse fibroblasts in vitro (Cai et al., 1998), and this effect on G-CSF production appears to be independent of the activation of tyrosine kinase. The increase in G-CSF by IL-17A is associated with an increase in neutrophil progenitors in vitro (Fossiez et al., 1996). In contrast, IL-17D, which induces GM-CSF and IL-6, but not G-CSF, in human venous endothelial cells actually suppresses the colony formation of neutrophil progenitors in vitro (Starnes et al., 2002). Furthermore, unlike IL-17A, IL-17F does not support proliferation of granulo-

cyte precursors in vitro (Starnes et al., 2001) despite a similar potency to IL-17A in the recruitment of neutrophils into the lungs of mice in vivo (Hurst et al., 2002).

Functional Interactions with Other Cytokines. The fact that responses to IL-17A can functionally interact with responses to other cytokines is very likely to have bearing for several inflammatory diseases. For example, costimulation of human airway epithelial cells with TNF-α enhances the release of CXCL8 and CXCL1, compared with the effect of IL-17A alone (Laan et al., 1999; Jones and Chan, 2002). There is also evidence of IL-17A synergizing with TNF-α in causing de novo synthesis CXCL1 in human mesothelial cells in vitro, which may be due to an increased stability of CXCL1 mRNA (Witowski et al., 2000). Furthermore, in rat intestinal epithelial cells in vitro, IL-17A and IL-1β synergize in activating the promoter of the C-X-C chemokine CINC (Awane et al., 1999). In addition, costimulation with IL-17A and the Th1 cytokine IFN-γ enhances the CXCL8 response compared with IL-17A alone in human bronchial epithelial cells in vitro as well (Kawaguchi et al., 2001a). Interestingly, certain cytokines typically implicated in Th2-like conditions (i.e., IL-4 and IL-13) enhance the CXCL8 response to IL-17A in human bronchial epithelial cells in vitro (Kawaguchi et al., 2001a). Similar to the case for CXCL8, the release of the colony-stimulating factors G-CSF and GM-CSF, is enhanced by costimulation with TNF-α and IL-17A in human bronchial epithelial cells in vitro (Jones and Chan, 2002; Laan et al., 2003). Of potential importance for neutrophil recruitment into the bronchoalveolar space, costimulation with IL-17A and IFN-γ markedly enhances intercellular adhesion molecule (ICAM)-1 protein in human bronchial epithelial cells, even though IL-17A has no effect of ICAM-1 expression when used as costimulation with IL-4 or IL-13 (Kawaguchi et al., 2001a). Given the fact that IL-17B and IL-17C are potent inducers of TNF-α and IL-1β (Li et al., 2000), it can be speculated that there are synergistic proinflammatory activities in between the different IL-17 family members.

Studies In Vivo

Immune Cell Recruitment. IL-17A lacks a direct effect on chemotaxis for human blood neutrophils in vitro, whereas it causes a substantial accumulation of neutrophils in a compartmentalized fashion in the bronchoalveolar and joint space of rats and mice in vivo (Ye et al., 2001a; Laan et al., 1999; Miyamoto et al., 2003; Hoshino et al., 1999, 2000). This in vivo response to rIL-17A in the bronchoalveolar space in vivo is blocked by a neutralizing and specific anti-IL-17 antibody (Laan et al., 1999) in addition to pretreatment with glucocortocoids (Laan et al., 1999). Expression of IL-17C, IL-17E, and IL-17F also result in significant neutrophil recruitment into the lung, whereas IL-17E also resulted in significant emigration of eosinophils (Hurst et al., 2002) consistent with its Th2 cytokine profile. Furthermore, forced expression of IL-17E (IL-25) results in increased eosinophilia, IgE, IL-4, IL-5, and IL-13 production, resulting in multiorgan inflammation (Pan et al., 2001; Kim et al., 2002). Similar findings have been reported by Fort and colleagues where overexpression of IL-17E resulted in hypertrophy of the duodenum, mucous accumulation, and eosinophilic inflammation of the gastrointestinal tract and lung (Fort et al., 2001). These findings were due to induction of IL-4 and IL-13, and subsequent IL-4/IL-13 signaling as overexpressing IL-17E in IL-4Rα knockout mice were protected from this gastrointestinal and lung pathology.

In line with its accumulating effect on neutrophils, local stimulation with IL-17A enhances the concentration of CXCL2 in the bronchoalveolar space of rats and mice in vivo (Laan et al., 1999; Ye et al., 2001a). In addition, IL-17A-induced release of CXCL1 also plays a role for neutrophil accumulation in the bronchoalveolar space of mice in vivo (Ferretti et al., 2003; Kolls et al., 2003). This is true for the potentially neutrophil-activating cytokine IL-6 as well (Hoshino et al., 1999). GM-CSF also appears to be involved in neutrophil accumulation caused by IL-17A in vivo, at least after costimulation with TNF-α (Laan et al., 2003). IL-17A may also regulate neurogenic inflammation as endogenous tachykinins enhance the IL-17A-induced neutrophil accumulation in the bronchoalveolar space of rats in vivo via NK-1 receptors (Hoshino et al., 1999). Interestingly, overexpression of IL-17A systemically results in massive extramedullary hematopoiesis in mice in vivo, caused by the induction of endogenous G-CSF and stem cell factor (SCF) (Schwarzenberger et al., 1998, 2000). Overexpression of IL-17A in the joint space of mice results in exacerbation of collagen-induced arthritis independent of IL-1β, and is associated with augmented neutrophil recruitment as well (Lubberts et al., 2001).

Local Neutrophil Activity. IL-17A can also activate neutrophils under certain conditions in vivo, even though this activation may be restricted to certain neutrophil proteases. Local administration of rIL-17A into the bronchoalveolar space causes a local increase in neutrophil elastase (NE) and myeloperoxidase (MPO) activity in rats in vivo (Hoshino et al., 2000). Despite these in vivo data, no corresponding effect on MPO is observed in isolated blood neutrophils from rats after stimulation with rIL-17A in vitro. The activating effect observed with IL-17A in vivo may therefore be mediated through indirect mechanisms, similar to what is the case for IL-17A's accumulating effect on neutrophils in organs in vivo. For comparison, given in a dose of that is equally potent to IL-17A in terms of neutrophil accumulation, rIL-1β does not increase NE or MPO activity after local administration in the bronchoalveolar space of rats in vivo (Hoshino et al., 2000). However, local costimulation with rIL-1β plus IL-17A, resulting in a similar magnitude of neutrophil accumulation, results in substantially more NE and MPO activity compared with IL-17A alone (Hoshino et al., 2000). This likely represents true synergism for IL-17A and IL-1β. However, the activating effect on neutrophils is not associated with a commensurate increase in matrix metalloproteinase (MMP)-9 as rIL-17A increases local MMP-9 no more than the number of neutrophils in the bronchoalveolar space of mice in vivo (Prause et al., 2004). Taken together, even though the exact mechanisms may differ for each proteolytic enzyme, these data indicate that IL-17A and likely, other IL-17 family members, are involved in determining the net proteolytic load locally in inflamed tissue (Prause et al., 2004).

Models of Joint Disease. The role of IL-17 family members in arthritis has recently been extensively reviewed (Lubberts, 2003). In line with IL-17A determining local proteolytic load, abrogation of IL-17A attenuates antigen-induced arthritis in mice in vivo (Bush et al., 2002;

Lubberts et al., 2004). Also, treatment with anti-IL-17A antibodies after the onset of experimental, collagen-induced arthritis decreases radiologic joint damage and histologic destruction of cartilage and bone as well as reduces IL-6 in serum of mice in vivo (Lubberts et al., 2004). Thus, as judged from these studies, IL-17A and IL-17F may contribute to erosion of cartilage and bone in joint disease. In line with this idea, the loss of the proximal regulator IL-23 is protective in autoimmune arthritis in mice, whereas in contrast, the loss of IL-12 is associated with exacerbated arthritis and an increased number of IL-17A-secreting T lymphocytes as well (Murphy et al., 2003).

Models of Host Defense. Substantial evidence from mice in vivo support a critical role of endogenous IL-17s in neutrophil recruitment and host defense. IL-17A, and IL-17F, is induced in a dose- and time-dependent fashion in response to gram-negative bacteria such as *Klebsiella pneumoniae* (Ye et al., 2001a, 2001b). Similar results have been observed with endotoxin as well (Larsson et al., 2000). Mice lacking IL-17R succumb to bacteremia and early death after pulmonary challenge to *Klebsiella pneumoniae* (Ye et al., 2001b). This is likely due to remarkably diminished recruitment of neutrophils into the bronchoalveolar space related to a reduced splenic granulopoeitic response to the infection and attenuation of local G-CSF production (Ye et al., 2001b). In confirmation of data in the IL-17R knockout mouse, antibody neutralization of IL-17A significantly attenuates neutrophil accumulation after local administration of endotoxin administration in the lung (Miyamoto et al., 2003; Ferretti et al., 2003).

Furthermore, endogenous IL-17A, released mainly by $CD4^+$ T-lymphocytes, also plays a critical role in orchestrating the formation of intra-abdominal abscesses and neutrophil accumulation in response to the gram-negative bacteria *Bacteroides fragilis* in vivo (Chung et al., 2003). The in vivo mechanisms involved in the abscess formation include costimulation of T lymphocytes via the CD28-B7 pathway, and the abscess formation is paralleled by a local increase in IL-17A protein, depending upon STAT 4 signaling (Chung et al., 2003). Systemic pretreatment with a specific and neutralizing anti-IL-17A antibody attenuates abscess formation. Taken together, IL-17A and IL-17F constitute crucial factors produced by T lymphocytes in orchestrating the neutrophil component of innate immunity during host defense. In addition, the expression pattern of IL-17RB in the gastrointestinal tract is compatible with a role for IL-17B and IL-17E in host defense/inflammation of the gut as well (Shi et al., 2000; Lee et al., 2001).

Models of Allergy and Adaptive Immunity. IL-17A also regulates neutrophil recruitment in response to allergen in the bronchoalveolar space as well. In ovalbumin-sensitized mice, airway allergen challenge is followed by de novo synthesis of IL-17A in the lungs (Hellings et al., 2003). Moreover, abrogation of endogenous IL-17A significantly attenuates allergen-induced neutrophil accumulation in the bronchoalveolar space of mice in vivo (Hellings et al., 2003). Interestingly, the referred abrogation of IL-17A increases IL-5 and eosinophil accumulation in the same compartment as well. These data suggest that IL-17A is involved in determining the balance between neutrophil and eosinophil accumulation after exposure to allergen. However, it remains unclear whether blocking endogenous IL-17A alters the generation of antigen-specific $CD4^+$ T-lymphocytes in mice in vivo (Hellings et al., 2003). Indeed, one study in IL-17A knockout mice does suggest that IL-17A is critical for proliferation of $CD4^+$ T-lymphocytes with a Th2 profile, as well as for IL-4 and IL-5 production, and for specific bronchial hyper-responsiveness to allergen (Nakae et al., 2002).

IL-17E, with its unique immunological profile, causes eosinophil accumulation in the bronchoalveolar space and nonspecific bronchial hyperreactivity, accompanied by a local increase in mRNA for IL-5, IL-13, IFN-γ, CXCL5 (LIX), and CCL11 (Eotaxin) in mice in vivo (Hurst et al., 2002; Fort et al., 2001). These observations clearly illustrate the fundamental functional differences among different members within the IL-17 cytokine family. The precise role of endogenous IL-17B, IL-17C, IL-17D, and IL-17F needs to be further defined.

Models of Malignancy. Both human cervical cancer and murine fibrosarcoma cell lines from that are transfected with the IL-17A cDNA show significantly greater tumor formation in vivo in nude mice and C57BL/6 mice, respectively (Tartour et al., 1999; Numasaki et al., 2003). In line with this, induced expression of IL-17A enhances angiogenesis within a model of fibrosarcoma tumors in mice (Numasaki et al., 2003). Whereas IL-17A stimulates endothelial cord formation and the secretion of VEGF, PGE1, and PGE2 in murine lung fibroblasts from in vitro (Numasaki et al., 2003, 2004), it has no effect on cellular proliferation on human cervical carcinoma cells in vitro (Tartour et al., 1999). However, overexpression of IL-17A increases macrophage recruitment in cervical cancer (Tartour et al., 1999). Finally, IL-17A increases cytotoxic T lymphocyte generation in an immunocompetent myeloid malignancy model in mice (Benchetrit et al., 2002). Interestingly, IL-17F, being similar to IL-17A, inhibits vessel tube formation in human umbilical venous endothelial cells (Starnes et al., 2001). IL-17 family members may thus exert both pro- or antitumor effects, depending on the immunogenicity of the tumor, the immune status of the host, and the angiogenic activity of the IL-17 family member.

Studies in Humans. There are now several clues to the potential role of the IL-17 family of cytokines in human lung disease. Healthy human volunteers with induced, severe airway inflammation due to the exposure to a swine confinement, display a pronounced increase in the concentration of free, soluble IL-17A protein in the bronchoalveolar space (Laan et al., 2002). This is associated with a local accumulation of neutrophils and lymphocytes as well. However, it is not known how these events relate to the increased long-term morbidity in lung disease among swine farmers (Reynolds et al., 1996). In further support of IL-17A being involved in lung disease, patients with mild asthma display a detectable increase in the local concentration of free, soluble IL-17A protein (Molet et al., 2001). Moreover, there is an association between asthma and an increase in immunoreactivity for intracellular IL-17A protein in inflammatory cells from the bronchoalveolar space. Compatible with this, a study on nasal polyps has shown an increased subepithelial expression of IL-17A among atopic patients (Molet et al., 2003). A study analyzing

induced sputum from patients with either asthma or chronic obstructive pulmonary disease (COPD) claims that there is no substantial difference in the concentration of free, soluble IL-17A for asthma compared with healthy airways, although IL-17A levels were higher in asthma than in COPD (Barczyk et al., 2003). In spite of a small study population, a positive correlation between local IL-17A and nonspecific bronchial responsiveness was shown when the sample size was pooled for analysis. In addition to this, a recent study demonstrated that allergen challenge can increase local IL-17F (ML-1) in patients with allergic asthma (Kawaguchi et al., 2001b). Interestingly, the "Th2-biased" IL-17 family member, IL-17E, displays a local increase in acute sinusitis (Casado et al., 2004). Despite these observations, there are no reports of IL-17E in asthma to date.

There are increasing data supporting a role of IL-17 family members in autoimmunity. Patients with inflammatory bowel disease display an elevated expression of IL-17A mRNA and intracellular protein in the intestinal mucosa (Fujino et al., 2003). Specifically, this is true in the colonic mucosa of patients with either ulcerative colitis or Crohn's disease when compared with corresponding samples from normal subjects or patients with infectious or ischemic colitis (Fujino et al., 2003). IL-17A expression is augmented in gut tissue and detectable in the serum of patients with active exacerbations of inflammatory bowel disease. In arthritis, IL-17A regulates proteinases with the potential to destroy local tissue. IL-17 releases MMP-1 in the joint synovium of patients with rheumatoid arthritis (Chabaud et al., 2000). The same is true for the regulation of MMP-13 in human osteoblasts in vitro. (Rifas and Arackal, 2003). Thus, both preclinical and human studies support IL-17 family members as therapeutic targets in rheumatoid arthritis (Lubberts, 2003). Lastly, IL-17A is upregulated in central nervous system lesions of patients with multiple sclerosis (MS) (Lock et al., 2002). As it has been recently been reported that IL-23 rather than IL-12 is more critical in the development of experimental autoimmune encephalitis in mice, a model of human MS (Cua et al., 2003). These data support the possibility of a IL-23:IL-17A/F axis in MS as well.

Finally, there are also some clues to the role of the IL-17 family of cytokines and their receptors in human cancer. Overexpression of IL-17RB is linked to nonrecurrence after tamoxifen chemoprophylaxis in hormone receptor-positive breast cancer (Ma et al., 2004), thus pointing out a potential involvement of its known ligands, IL-17B and IL-17E respectively (Shi et al., 2000; Lee et al., 2001). A corresponding involvement for IL-17C is indicated by the observation that the expression of IL-17RC is downregulated in prostate cancer (Moseley et al., 2003). As these receptors show significant alternative splicing, understanding the respective roles of these receptors in tumorigenesis and angiogenesis will be complex and will most likely require major research efforts in the future.

Conclusions

There is currently experimental and clinical evidence that IL-17 family members are involved in specific inflammatory processes leading to the mobilization of granulocytes. To date, most published evidence supports a role for IL-17A, and possibly IL-17F, as a promoter of granulopoeisis, neutrophil accumulation, and neutrophil activation in the lung, joint space, central nervous system, and intestinal tissue. The production of IL-17A and IL-17F by T lymphocytes is regulated proximally by IL-23 produced by dendritic cells, independently of cell-to-cell contact or traditional TCR activation (Figure 2). This places IL-17A, and most likely IL-17F as well, as an important player in host defense and autoimmunity. Thus, IL-17A and IL-17F may be uniquely positioned at the interface of adapted and innate immunity. Moreover, IL-17B and IL-17C may exert a cooperative proinflammatory action together with IL-17A and IL-17F by regulating TNF-α and IL-1β release, which can potentiate the effects of IL-17A and IL-17F on the local the secretion of C-X-C chemokines and growth factors in tissue. Furthermore, IL-17E with is Th2 profile provides a strong rationale to further characterizing this IL-17 family member in allergic disease. In addition, the extensive and specific distribution patterns of the individual receptor subtypes for the IL-17 family members are compatible with their involvement in a wide range of inflammatory diseases. Future studies in humans should further elucidate the potential therapeutic utility of drugs targeting IL-17 family members and their receptors in inflammatory and neoplastic disease.

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Selected Reading

Aggarwal, S., Ghilardi, N., Xie, M.H., De Sauvage, F.J., and Gurney, A.L. (2003). Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. J. Biol. Chem. *278*, 1910–1914.

Awane, M., Andres, P.G., Li, D.J., and Reinecker, H.C. (1999). NF-kappa B-inducing kinase is a common mediator of IL-17-, TNF-alpha-, and IL-1 beta-induced chemokine promoter activation in intestinal epithelial cells. J. Immunol. *162*, 5337–5344.

Barczyk, A., Pierzchala, W., and Sozanska, E. (2003). Interleukin-17 in sputum correlates with airway hyperresponsiveness to methacholine. Respir. Med. *97*, 726–733.

Benchetrit, F., Ciree, A., Vives, V., Warnier, G., Gey, A., Sautes-Fridman, C., Fossiez, F., Haicheur, N., Fridman, W.H., and Tartour, E. (2002). Interleukin-17 inhibits tumor cell growth by means of a T-cell-dependent mechanism. Blood *99*, 2114–2121.

Bush, K.A., Farmer, K.M., Walker, J.S., and Kirkham, B.W. (2002). Reduction of joint inflammation and bone erosion in rat adjuvant arthritis by treatment with interleukin-17 receptor IgG1 Fc fusion protein. Arthritis Rheum. *46*, 802–805.

Cai, X.Y., Gommoll, C.P.J., Justice, L., Narula, S.K., and Fine, J.S. (1998). Regulation of granulocyte colony-stimulating factor gene expression by interleukin-17. Immunol. Lett. *62*, 51–58.

Casado, B., Pannell, L.K., Viglio, S., Iadarola, P., and Baraniuk, J.N. (2004). Analysis of the sinusitis nasal lavage fluid proteome using

capillary liquid chromatography interfaced to electrospray ionization-quadrupole time of flight- tandem mass spectrometry. Electrophoresis *25*, 1386–1393.

Chabaud, M., Garnero, P., Dayer, J.M., Guerne, P.A., Fossiez, F., and Miossec, P. (2000). Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis. Cytokine *12*, 1092–1099.

Chen, Y., Thai, P., Zhao, Y.H., Ho, Y.S., DeSouza, M.M., and Wu, R. (2003). Stimulation of airway mucin gene expression by interleukin (IL)-17 through IL-6 paracrine/autocrine loop. J. Biol. Chem. *278*, 17036–17043.

Chung, D.R., Kasper, D.L., Panzo, R.J., Chitnis, T., Grusby, M.J., Sayegh, M.H., and Tzianabos, A.O. (2003). CD4+ T cells mediate abscess formation in intra-abdominal sepsis by an IL-17-dependent mechanism. J. Immunol. *170*, 1958–1963.

Clark, H.F., Gurney, A.L., Abaya, E., Baker, K., Baldwin, D., Brush, J., Chen, J., Chow, B., Chui, C., Crowley, C., et al. (2003). The secreted protein discovery initiative (SPDI), a large-scale effort to identify novel human secreted and transmembrane proteins: a bioinformatics assessment. Genome Res. *13*, 2265–2270.

Cua, D.J., Sherlock, J., Chen, Y., Murphy, C.A., Joyce, B., Seymour, B., Lucian, L., To, W., Kwan, S., Churakova, T., et al. (2003). Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature *421*, 744–748.

Ferretti, S., Bonneau, O., Dubois, G.R., Jones, C.E., and Trifilieff, A. (2003). IL-17, produced by lymphocytes and neutrophils, is necessary for lipopolysaccharide-induced airway neutrophilia: IL-15 as a possible trigger. J. Immunol. *170*, 2106–2112.

Fort, M.M., Cheung, J., Yen, D., Li, J., Zurawski, S.M., Lo, S., Menon, S., Clifford, T., Hunte, B., Lesley, R., et al. (2001). IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies in vivo. Immunity *15*, 985–995.

Fossiez, F., Djossou, O., Chomarat, P., Flores-Romo, L., Ait-Yahia, S., Maat, C., Pin, J.J., Garrone, P., Garcia, E., Saeland, S., et al. (1996). T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. J. Exp. Med. *183*, 2593–2603.

Fujino, S., Andoh, A., Bamba, S., Ogawa, A., Hata, K., Araki, Y., Bamba, T., and Fujiyama, Y. (2003). Increased expression of interleukin 17 in inflammatory bowel disease. Gut *52*, 65–70.

Happel, K.I., Zheng, M., Young, E., Quinton, L.J., Lockhart, E., Ramsay, A.J., Shellito, J.E., Schurr, J.R., Bagby, G.J., Nelson, S., and Kolls, J.K. (2003). Cutting edge: roles of Toll-like receptor 4 and IL-23 in IL-17 expression in response to Klebsiella pneumoniae infection. J. Immunol. *170*, 4432–4436.

Harper, R., Wu, K., Chang, M.M., Yoneda, K., Pan, R., Reddy, S.P., and Wu, R. (2001). Activation of nuclear factor-kappa b transcriptional activity in airway epithelial cells by thioredoxin but not by N-acetyl-cysteine and glutathione. Am. J. Respir. Cell Mol. Biol. *25*, 178–185.

Haudenschild, D., Moseley, T., Rose, L., and Reddi, A.H. (2002). Soluble and transmembrane isoforms of novel interleukin-17 receptor-like protein by RNA splicing and expression in prostate cancer. J. Biol. Chem. *277*, 4309–4316.

Hellings, P.W., Kasran, A., Liu, Z., Vandekerckhove, P., Wuyts, A., Overbergh, L., Mathieu, C., and Ceuppens, J.L. (2003). Interleukin-17 orchestrates the granulocyte influx into airways after allergen inhalation in a mouse model of allergic asthma. Am. J. Respir. Cell Mol. Biol. *28*, 42–50.

Hoshino, H., Lötvall, J., Skoogh, B.E., and Lindén, A. (1999). Neutrophil recruitment by interleukin-17 into rat airways in vivo. Role of tachykinins. Am. J. Respir. Crit. Care Med. *159*, 1423–1428.

Hoshino, H., Laan, M., Sjöstrand, M., Lötvall, J., Skoogh, B.E., and Lindén, A. (2000). Increased elastase and myeloperoxidase activity associated with neutrophil recruitment by IL-17 in airways in vivo. J. Allergy Clin. Immunol. *105*, 143–149.

Hurst, S.D., Muchamuel, T., Gorman, D.M., Gilbert, J.M., Clifford, T., Kwan, S., Menon, S., Seymour, B., Jackson, C., Kung, T.T., et al. (2002). New IL-17 family members promote Th1 or Th2 responses in the lung: in vivo function of the novel cytokine IL-25. J. Immunol. *169*, 443–453.

Hwang, S.Y., Kim, J.Y., Kim, K.W., Park, M.K., Moon, Y., Kim, W.U., and Kim, H.Y. (2004). IL-17 induces production of IL-6 and IL-8 in rheumatoid arthritis synovial fibroblasts via NF-kappaB- and PI3-kinase/Akt-dependent pathways. Arthritis Res. Ther. *6*, R120–R128.

Hymowitz, S.G., Filvaroff, E.H., Yin, J.P., Lee, J., Cai, L., Risser, P., Maruoka, M., Mao, W., Foster, J., Kelley, R.F., et al. (2001). IL-17s adopt a cystine knot fold: structure and activity of a novel cytokine, IL-17F, and implications for receptor binding. EMBO J. *20*, 5332–5341.

Infante-Duarte, C., Horton, H.F., Byrne, M.C., and Kamradt, T. (2000). Microbial lipopeptides induce the production of IL-17 in Th cells. J. Immunol. *165*, 6107–6115.

Jones, C.E., and Chan, K. (2002). Interleukin-17 stimulates the expression of interleukin-8, growth-related oncogene-alpha, and granulocyte-colony-stimulating factor by human airway epithelial cells. Am. J. Respir. Cell Mol. Biol. *26*, 748–753.

Jovanovic, D.V., Di Battista, J.A., Martel-Pelletier, J., Jolicoeur, F.C., He, Y., Zhang, M., Mineau, F., and Pelletier, J.P. (1998). IL-17 stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages. J. Immunol. *160*, 3513–3521.

Kawaguchi, M., Kokubu, F., Kuga, H., Matsukura, S., Hoshino, H., Ieki, K., Imai, T., Adachi, M., and Huang, S.K. (2001a). Modulation of bronchial epithelial cells by IL-17. J. Allergy Clin. Immunol. *108*, 804–809.

Kawaguchi, M., Onuchic, L.F., Li, X.D., Essayan, D.M., Schroeder, J., Xiao, H.Q., Liu, M.C., Krishnaswamy, G., Germino, G., and Huang, S.K. (2001b). Identification of a novel cytokine, ML-1, and its expression in subjects with asthma. J. Immunol. *167*, 4430–4435.

Kennedy, T., Ghio, A.J., Reed, W., Samet, J., Zagorski, J., Quay, J., Carter, J., Dailey, L., Hoidal, J.R., and Devlin, R.B. (1998). Copper-dependent inflammation and nuclear factor-kappaB activation by particulate air pollution. Am. J. Respir. Cell Mol. Biol. *19*, 366–378.

Kim, M.R., Manoukian, R., Yeh, R., Silbiger, S.M., Danilenko, D.M., Scully, S., Sun, J., DeRose, M.L., Stolina, M., Chang, D., et al. (2002). Transgenic overexpression of human IL-17E results in eosinophilia, B-lymphocyte hyperplasia, and altered antibody production. Blood *100*, 2330–2340.

Kolls, J.K., Kanaly, S.T., and Ramsay, A.J. (2003). Interleukin-17: an emerging role in lung inflammation. Am. J. Respir. Cell Mol. Biol. *28*, 9–11.

Laan, M., Cui, Z.H., Hoshino, H., Lötvall, J., Sjöstrand, M., Gruenert, D.C., Skoogh, B.E., and Lindén, A. (1999). Neutrophil recruitment by human IL-17 via C–X–C chemokine release in the airways. J. Immunol. *162*, 2347–2352.

Laan, M., Lötvall, J., Chung, K.F., and Lindén, A. (2001). IL-17-induced cytokine release in human bronchial epithelial cells in vitro: role of mitogen-activated protein (MAP) kinases. Br. J. Pharmacol. *133*, 200–206.

Laan, M., Palmberg, L., Larsson, K., and Lindén, A. (2002). Free, soluble interleukin-17 protein during severe inflammation in human airways. Eur. Respir. J. *19*, 534–537.

Laan, M., Prause, O., Miyamoto, M., Sjöstrand, M., Hytonen, A.M., Kaneko, T., Lötvall, J., and Lindén, A. (2003). A role of GM-CSF in the accumulation of neutrophils in the airways caused by IL-17 and TNF-alpha. Eur. Respir. J. *21*, 387–393.

Larsson, R., Rocksen, D., Lilliehook, B., Jonsson, A., and Bucht, A. (2000). Dose-dependent activation of lymphocytes in endotoxin-induced airway inflammation. Infect. Immun. *68*, 6962–6969.

Lee, J., Ho, W.H., Maruoka, M., Corpuz, R.T., Baldwin, D.T., Foster, J.S., Goddard, A.D., Yansura, D.G., Vandlen, R.L., Wood, W.I., and Gurney, A.L. (2001). IL-17E, a novel proinflammatory ligand for the IL-17 receptor homolog IL-17Rh1. J. Biol. Chem. *276*, 1660–1664.

Li, H., Chen, J., Huang, A., Stinson, J., Heldens, S., Foster, J., Dowd, P., Gurney, A.L., and Wood, W.I. (2000). Cloning and characterization of IL-17B and IL-17C, two new members of the IL-17 cytokine family. Proc. Natl. Acad. Sci. USA *97*, 773–778.

Lock, C., Hermans, G., Pedotti, R., Brendolan, A., Schadt, E., Garren, H., Langer-Gould, A., Strober, S., Cannella, B., Allard, J., et al. (2002).

Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. Nat. Med. *8*, 500–508.

Lubberts, E. (2003). The role of IL-17 and family members in the pathogenesis of arthritis. Curr. Opin. Investig. Drugs *4*, 572–577.

Lubberts, E., Joosten, L.A., Oppers, B., Van Den, B.L., Coenen-De Roo, C.J., Kolls, J.K., Schwarzenberger, P., van De Loo, F.A., and Van den Berg, W.B. (2001). IL-1-Independent Role of IL-17 in Synovial Inflammation and Joint Destruction During Collagen-Induced Arthritis. J. Immunol. *167*, 1004–1013.

Lubberts, E., Koenders, M.I., Oppers-Walgreen, B., Van Den, B.L., Coenen-De Roo, C.J., Joosten, L.A., and Van den Berg, W.B. (2004). Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion. Arthritis Rheum. *50*, 650–659.

Ma, X.J., Wang, Z., Ryan, P.D., Isakoff, S.J., Barmettler, A., Fuller, A., Muir, B., Mohapatra, G., Salunga, R., Tuggle, J.T., et al. (2004). A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. Cancer Cell *5*, 607–616.

Miyamoto, M., Prause, O., Sjöstrand, M., Laan, M., Lötvall, J., and Lindén, A. (2003). Endogenous IL-17 as a Mediator of Neutrophil Recruitment Caused by Endotoxin Exposure in Mouse Airways. J. Immunol. *170*, 4665–4672.

Molet, S., Hamid, Q., Davoine, F., Nutku, E., Taha, R., Page, N., Olivenstein, R., Elias, J., and Chakir, J. (2001). IL-17 is increased in asthmatic airways and induces human bronchial fibroblasts to produce cytokines. J. Allergy Clin. Immunol. *108*, 430–438.

Molet, S.M., Hamid, Q.A., and Hamilos, D.L. (2003). IL-11 and IL-17 expression in nasal polyps: relationship to collagen deposition and suppression by intranasal fluticasone propionate. Laryngoscope *113*, 1803–1812.

Moore, E.E., Presnell, S., Garrigues, U., Guilbot, A., LeGuern, E., Smith, D., Yao, L., Whitmore, T.E., Gilbert, T., Palmer, T.D., et al. (2002). Expression of IL-17B in neurons and evaluation of its possible role in the chromosome 5q-linked form of Charcot-Marie-Tooth disease. Neuromuscul. Disord. *12*, 141–150.

Mori, N., Oishi, K., Sar, B., Mukaida, N., Nagatake, T., Matsushima, K., and Yamamoto, N. (1999). Essential role of transcription factor nuclear factor-kappaB in regulation of interleukin-8 gene expression by nitrite reductase from Pseudomonas aeruginosa in respiratory epithelial cells. Infect. Immun. *67*, 3872–3878.

Moseley, T.A., Haudenschild, D.R., Rose, L., and Reddi, A.H. (2003). Interleukin-17 family and IL-17 receptors. Cytokine Growth Factor Rev. *14*, 155–174.

Murphy, C.A., Langrish, C.L., Chen, Y., Blumenschein, W., McClanahan, T., Kastelein, R.A., Sedgwick, J.D., and Cua, D.J. (2003). Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. J. Exp. Med. *198*, 1951–1957.

Nakae, S., Komiyama, Y., Nambu, A., Sudo, K., Iwase, M., Homma, I., Sekikawa, K., Asano, M., and Iwakura, Y. (2002). Antigen-Specific T Cell Sensitization Is Impaired in IL-17-Deficient Mice, Causing Suppression of Allergic Cellular and Humoral Responses. Immunity *17*, 375–387.

Numasaki, M., Fukushi, J., Ono, M., Narula, S.K., Zavodny, P.J., Kudo, T., Robbins, P.D., Tahara, H., and Lotze, M.T. (2003). Interleukin-17 promotes angiogenesis and tumor growth. Blood *101*, 2620–2627.

Numasaki, M., Lotze, M.T., and Sasaki, H. (2004). Interleukin-17 augments tumor necrosis factor-alpha-induced elaboration of proangiogenic factors from fibroblasts. Immunol. Lett. *93*, 39–43.

Oppmann, B., Lesley, R., Blom, B., Timans, J.C., Xu, Y., Hunte, B., Vega, F., Yu, N., Wang, J., Singh, K., et al. (2000). Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity *13*, 715–725.

Pan, G., French, D., Mao, W., Maruoka, M., Risser, P., Lee, J., Foster, J., Aggarwal, S., Nicholes, K., Guillet, S., et al. (2001). Forced expression of murine IL-17E induces growth retardation, jaundice, a Th2-biased response, and multiorgan inflammation in mice. J. Immunol. *167*, 6559–6567.

Prause, O., Laan, M., Lötvall, J., and Lindén, A. (2003). Pharmacological modulation of interleukin-17-induced GCP-2-, GRO-alpha- and interleukin-8 release in human bronchial epithelial cells. Eur. J. Pharmacol. *462*, 193–198.

Prause, O., Bozinovski, S., Anderson, G.P., and Lindén, A. (2004). Increased matrix metalloproteinase-9 concentration and activity after stimulation with interleukin-17 in mouse airways. Thorax *59*, 313–317.

Reynolds, S.J., Donham, K.J., Whitten, P., Merchant, J.A., Burmeister, L.F., and Popendorf, W.J. (1996). Longitudinal evaluation of dose-response relationships for environmental exposures and pulmonary function in swine production workers. Am. J. Ind. Med. *29*, 33–40.

Rifas, L., and Arackal, S. (2003). T cells regulate the expression of matrix metalloproteinase in human osteoblasts via a dual mitogen-activated protein kinase mechanism. Arthritis Rheum. *48*, 993–1001.

Rouvier, E., Luciani, M.F., Mattei, M.G., Denizot, F., and Golstein, P. (1993). CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpesvirus saimiri gene. J. Immunol. *150*, 5445–5456.

Schwarzenberger, P., La Russa, V., Miller, A., Ye, P., Huang, W., Zieske, A., Nelson, S., Bagby, G.J., Stoltz, D., Mynatt, R.L., et al. (1998). IL-17 stimulates granulopoiesis in mice: use of an alternate, novel gene therapy-derived method for in vivo evaluation of cytokines. J. Immunol. *161*, 6383–6389.

Schwarzenberger, P., Huang, W., Ye, P., Oliver, P., Manuel, M., Zhang, Z., Bagby, G., Nelson, S., and Kolls, J.K. (2000). Requirement of endogenous stem cell factor and granulocyte-colony-stimulating factor for IL-17-mediated granulopoiesis. J. Immunol. *164*, 4783–4789.

Shi, Y., Ullrich, S.J., Zhang, J., Connolly, K., Grzegorzewski, K.J., Barber, M.C., Wang, W., Wathen, K., Hodge, V., Fisher, C.L., et al. (2000). A novel cytokine receptor-ligand pair. Identification, molecular characterization, and in vivo immunomodulatory activity. J. Biol. Chem. *275*, 19167–19176.

Shin, H.C., Benbernou, N., Esnault, S., and Guenounou, M. (1999). Expression of IL-17 in human memory CD45RO+ T lymphocytes and its regulation by protein kinase A pathway. Cytokine *11*, 257–266.

Silva, W.A., Jr., Covas, D.T., Panepucci, R.A., Proto-Siqueira, R., Siufi, J.L., Zanette, D.L., Santos, A.R., and Zago, M.A. (2003). The profile of gene expression of human marrow mesenchymal stem cells. Stem Cells *21*, 661–669.

Starnes, T., Robertson, M.J., Sledge, G., Kelich, S., Nakshatri, H., Broxmeyer, H.E., and Hromas, R. (2001). Cutting edge: IL-17F, a novel cytokine selectively expressed in activated T cells and monocytes, regulates angiogenesis and endothelial cell cytokine production. J. Immunol. *167*, 4137–4140.

Starnes, T., Broxmeyer, H.E., Robertson, M.J., and Hromas, R. (2002). Cutting edge: IL-17D, a novel member of the IL-17 family, stimulates cytokine production and inhibits hemopoiesis. J. Immunol. *169*, 642–646.

Tartour, E., Fossiez, F., Joyeux, I., Galinha, A., Gey, A., Claret, E., Sastre-Garau, X., Couturier, J., Mosseri, V., Vives, V., et al. (1999). Interleukin *17*, a T-cell-derived cytokine, promotes tumorigenicity of human cervical tumors in nude mice. Cancer Res. *59*, 3698–3704.

Trinchieri, G., Pflanz, S., and Kastelein, R.A. (2003). The IL-12 family of heterodimeric cytokines: new players in the regulation of T cell responses. Immunity *19*, 641–644.

Vanaudenaerde, B.M., Wuyts, W.A., Dupont, L.J., Van Raemdonck, D.E., Demedts, M.M., and Verleden, G.M. (2003). Interleukin-17 stimulates release of interleukin-8 by human airway smooth muscle cells in vitro: a potential role for interleukin-17 and airway smooth muscle cells in bronchiolitis obliterans syndrome. J. Heart Lung Transplant. *22*, 1280–1283.

Witowski, J., Pawlaczyk, K., Breborowicz, A., Scheuren, A., Kuzlan-Pawlaczyk, M., Wisniewska, J., Polubinska, A., Friess, H., Gahl, G.M., Frei, U., and Jorres, A. (2000). IL-17 stimulates intraperitoneal neutrophil infiltration through the release of GRO alpha chemokine from mesothelial cells. J. Immunol. *165*, 5814–5821.

Yang, R.B., Ng, C.K., Wasserman, S.M., Komuves, L.G., Gerritsen,

M.E., and Topper, J.N. (2003). A novel interleukin-17 receptor-like protein identified in human umbilical vein endothelial cells antagonizes basic fibroblast growth factor-induced signaling. J. Biol. Chem. *278*, 33232–33238.

Yao, Z., Fanslow, W.C., Seldin, M.F., Rousseau, A.-M., Painter, S.L., Comeau, M.R., Cohen, J.I., and Spriggs, M.K. (1995). Herpesvirus saimiri encodes a new cytokine, IL-17, which binds to novel cytokine receptor. Immunity *3*, 811–821.

Ye, P., Garvey, P.B., Zhang, P., Nelson, S., Bagby, G., Summer, W.R., Schwarzenberger, P., Shellito, J.E., and Kolls, J.K. (2001a). Interleukin-17 and Lung Host Defense against Klebsiella pneumoniae Infection. Am. J. Respir. Cell Mol. Biol. *25*, 335–340.

Ye, P., Rodriguez, F.H., Kanaly, S., Stocking, K.L., Schurr, J., Schwarzenberger, P., Oliver, P., Huang, W., Zhang, P., Zhang, J., et al. (2001b). Requirement of interleukin 17 receptor signaling for lung cxc chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. J. Exp. Med. *194*, 519–528.

Ziolkowska, M., Koc, A., Luszczykiewicz, G., Ksiezopolska-Pietrzak, K., Klimczak, E., Chwalinska-Sadowska, H., and Maslinski, W. (2000). High levels of IL-17 in rheumatoid arthritis patients: IL-15 triggers in vitro IL-17 production via cyclosporin A-sensitive mechanism. J. Immunol. *164*, 2832–2838.