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# The Biological Functions of T Helper 17 Cell Effector Cytokines in Inflammation

**Wenjun Ouyang**[1,*], **Jay K. Kolls**[2,*], and **Yan Zheng**[3]

[1]Department of Immunology, Genentech, 1 DNA Way, South San Francisco, California 94080, USA

[2]Division of Pulmonary Medicine, Allergy, and Immunology, Department of Pediatrics, Children's Hospital of Pittsburgh and The University of Pittsburgh, Pittsburgh, PA 15213, USA

[3]Inflammation Pathways Group, Pfizer Global Research and Development, St. Louis Laboratories, 700 Chesterfield Parkway West, Chesterfield, Missouri 63017, USA

## Abstract

T helper 17 (Th17) cells belong to a recently identified T helper subset, in addition to the traditional Th1 and Th2 subsets. These cells are characterized as preferential producers of interleukin-17A (IL-17A), IL-17F, IL-21, and IL-22. Th17 cells and their effector cytokines mediate host defensive mechanisms to various infections, especially extracellular bacteria infections, and are involved in the pathogenesis of many autoimmune diseases. The receptors for IL-17 and IL-22 are broadly expressed on various epithelial tissues. The effector cytokines of Th17 cells, therefore, mediate the crucial crosstalk between immune system and tissues, and play indispensable roles in tissue immunity.

## Introduction

The T helper 1 (Th1) cell and Th2 cell paradigm, first proposed by Mosmann and Coffman, has been used to explain how hosts elicit different adaptive immune responses to eradicate the evasion of various pathogens (Glimcher and Murphy, 2000; Mosmann and Coffman, 1989). Upon first encounter of foreign antigens presented by antigen-presenting cells (APCs), naïve $CD4^+$ T cells can differentiate into either interferon-γ (IFN-γ)-producing Th1 cells or IL-4-producing Th2 cells, and this differentiation is largely controlled by various environmental factors, especially by signals coming directly from APCs (Glimcher and Murphy, 2000). Proper T helper cell responses are essential for the hosts to orchestrate sufficient defensive mechanisms to control infections. For example, Th1 cells enhance the cellular immunity against virus or intracellular pathogens, such as *Leishmania major* (Sacks and Noben-Trauth, 2002), whereas Th2 cells are important for humoral immunity and control of helminth infections (Anthony et al., 2007).

Uncontrolled and persistent effector T cell responses, however, can drive the onset of autoimmunity, allergy, or atopy. Evidence from clinical observations and from studies on experimental animals supports the idea that uncontrolled Th2 cell responses, as well downstream cytokines IL-4, IL-5, and IL-13, are underlying the development of atopic diseases, such as asthma (Cohn et al., 2004). In addition, abnormal Th1 cell responses have been demonstrated to mediate, at least in part, many other autoimmune diseases, including psoriasis and inflammatory bowel disease (IBD) (Bouma and Strober, 2003; Lowes et al.,



*Correspondence: jay.kolls@chp.edu (J.K.K.), ouyang.wenjun@gene.com (W.O.).

2007). It has also become clear, however, that many complicated pathological situations cannot be simply explained by the Th1 cell and Th2 cell paradigm. Efforts to resolve these issues in recent years have resulted in the discovery of many new T helper cell subsets, including Treg cell and Th17 cell subsets (see commentary by Locksley [2008], in this issue of *Immunity*).

Initially, Th1 cells had been speculated to play the major pathological functions in preclinical experimental allergic encephalitis (EAE) models, which were used broadly for studying human multiple sclerosis (MS), primarily based on the in vivo data in which the IL-12 p40 subunit was either ablated or blocked (Kastelein et al., 2007). This view has been dramatically changed after the discovery of IL-23, a cytokine that consists of a unique p19 subunit and shares a common p40 subunit with IL-12 (Oppmann et al., 2000). In vivo studies from Cua and colleagues convincingly demonstrated that it was IL-23, but not IL-12, that played an essential role in the pathogenesis of myelin oligodendrocyte glycoprotein (MOG)-induced EAE (Cua et al., 2003) During the late 1990s, the discovery of new cytokines was facilitated by the human genome project. Many cytokines have been identified, including the IL-17-family cytokines and new cytokine members in the IL-10 family (Pestka et al., 2004; Weaver et al., 2007). Among these cytokines, IL-17A and IL-22 were soon realized to be T cell cytokines and to have important functions in inflammatory responses (Dumoutier et al., 2000a; Yao et al., 1995). In 2000, Infante-Duarte and colleagues suggested that IL-17A-producing $CD4^+$ T cells might represent a unique T helper cell subset that was different from the classic Th1 cell and Th2 cell subsets (Infante-Duarte et al., 2000). In their studies, they demonstrated that naïve T cells primed by lysate of *B. burgdorfei* developed a phenotype with much higher IL-17A production than those from T cells primed under Th1 and Th2 conditions. They suggested that IL-6 might play a role in the development of these IL-17A-producing T helper cells (Infante-Duarte et al., 2000). Consistent with these results, IL-17A produced by $CD4^+$ T cells is indispensable for host defense against *Klebsiella pneumonia* infection, an extracellular bacterial infection that is not fully controlled by either Th1 or Th2 cells (Ye et al., 2001). Gurney's group later established the potential link between IL-23 and these IL-17A producing T cells in vitro by showing that IL-23 enhanced IL-17 production from memory $CD4^+$ T cells but not from naïve $CD4^+$ T cells (Aggarwal et al., 2003). This link was further confirmed by the elegant in vivo experiments performed by Cua's group, who demonstrated that IL-23-primed Th17 cells were much more pathogenic in EAE models than were IL-12-primed Th1 cells (Langrish et al., 2005). On the basis of these pioneering studies, Th17 cells have been quickly recognized as a distinct T helper cell population that plays a crucial roles in $CD4^+$ T cell-mediated adaptive immunity. In the past two years, a wealth of research has further revealed the regulatory and functional roles of these Th17 cells in both mouse and human systems. In addition to IL-17A, IL-17F, IL-22, and IL-21 have all been identified as effector cytokines that are preferentially produced by this T cell subset. In this review, we focus our discussion on the biological functions of these effector cytokines of Th17 cells in inflammatory responses.

## IL-17A and IL-17F

IL-17A was originally cloned and described by Rouvier et. al. and named CTLA8 (Rouvier et al., 1993). It was subsequently renamed IL-17 and, more recently, IL-17A. IL-17A was also cloned by Immunex and found to share 58% homology with an open reading frame of the T-lymphotropic Herpesvirus Samirii virus (viral IL-17). IL-17A is the founding member of the IL-17 family of cytokines, which has five other family members, designated IL-17A–F. IL-17A is disulfide-linked homodimeric glycoprotein, consisting of 155 amino acids (Yao et al., 1995), exerting part of its actions as a homodimer with a molecular weight around 35 kiloDalton (kDa). All members of the IL-17 family show conservation in their c-termini

with five spatially conserved cysteine residues, accounting for a characteristic cysteine-knot formation for IL-17A and F (Hymowitz et al., 2001). IL-17F shares the greatest homology (55%) with IL-17A. Both IL-17A and IL-17F are produced by Th17 cells, whereas the other IL-17 family members, IL-17B, IL-17C, and IL-17D, are produced by non-T cell sources. IL-17A and IL-17F can either exist as IL-17A homodimers and IL-17F homodimers or as IL-17A-IL-17F heterodimers (Liang et al., 2007). IL-17A homodimers are very efficient in inducing chemokine production by epithelial cells; Among these isoforms and controlling for molarity, IL-17A homodimers show the greatest potency in inducing chemokine expression in epithelial cells, followed by IL-17A–F heterodimers, followed by IL-17F homodimers (Liang et al., 2007). Using neutralizing antibodies for these specific isoforms, Liang et al. showed that neutralization of IL-17A homodimers strongly blocked neutrophilic airway inflammation mediated by adoptive transfer of ovalbumin-specific polarized Th17 cells and airway challenge with antigen. Again, neutralization of the IL-17A–F heterodimers shows intermediate efficacy in blocking airway inflammation, and neutralization of the IL-17F homodimers shows the least efficacy. Thus, in this model of airway-inflammation-blocking strategies targeting IL-17A and IL-17A–F, heterodimers might be the most efficacious (Liang et al., 2007). The contributions of these individual isoforms in autoimmune diseases such as EAE, colitis, or arthritis remain to be determined.

## IL-17RA, IL-17RC, and Signaling Pathways

The originally described IL-17 receptor (IL-17RA) (Yao et al., 1995) 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 mRNA for IL-17RA can be detected in epithelial cells, fibroblasts, B and T lymphocytes, myelomonocytic cells, and marrow stromal cells (Silva et al., 2003). The IL-17RA protein is present on peripheral blood T lymphocytes and in vascular endothelial cells from humans (Moseley et al., 2003). Mice with a homozygous deletion of the gene encoding IL-17RA have no detectable binding of IL-17A in B or T lymphocytes (Ye et al., 2001). Moreover, homozygous deletion of IL-17RA abrogates the increase in splenic neutrophil progenitors resulting from the overexpression of IL-17A (Ye et al., 2001) or IL-17F (unpublished observations). In human epithelial cells, a monoclonal antibody against IL-17RA effectively neutralizes both IL-17A- and IL-17F-induced expression of granulocyte-colony stimulating factor (G-CSF) and Chemokine (C-X-C motif) ligand 1 (CXCL1). However, a soluble form of IL-17RA is only effective in partially inhibiting IL-17A activity and is ineffective in blocking G-CSF and CXCL1 induced by IL-17F, suggesting that the cell surface receptor complex out-competes soluble IL-17RA (Jones and Chan, 2002; McAllister et al., 2005). Human IL-17RA binds IL-17A with a relatively low affinity. The binding potency is approximately one-tenth the potency of the cytokine response (IL-6 release) to IL-17A, which led to the hypothesis that there were likely additional receptors involved in IL-17A-induced cell signaling (Yao et al., 1995). IL-17RC, another Type I transmembrane receptor, is expressed in human prostate, cartilage, kidney, liver, heart, and muscle (Haudenschild et al., 2002; Moseley et al., 2003). Toy and colleagues have recently shown that IL-17RA and IL-17RC can be coimmunopreciptated and that the cotransfection of IL-17RA and IL-17RC results in effective binding of IL-17A and IL-17F and signaling as measured by the induction of CXCL1 (Toy et al., 2006). Furthermore, IL-17RC has been shown to be critical for binding and signaling in response to IL-17F homodimers. Importantly, fibroblasts generated from IL-17RC-deficient mice fail to respond to either IL-17A or IL-17F (Zheng et al., 2008). IL-17RC undergoes significant alternative splicing, with some forms that might still be capable of ligand binding and being secreted, thus potentially inhibiting IL-17 signaling (Haudenschild et al., 2002; Moseley et

al., 2003). Thus, both IL-17RA and IL-17RC chains are critical for signaling in response to IL-17A and IL-17F.

As mentioned above, both IL-17A and IL-17F induce granulpoietic factors (G-CSF and stem cell factor) and CXC chemokines: CXCL1, CXCL2, and CXCL5 in mouse fibroblasts and epithelial cells; and CXCL1, CXCL2, CXCL5, and CXCL8 in human epithelial cells (Fossiez et al., 1996; Jones and Chan, 2002; Kawaguchi et al., 2001; Laan et al., 1999; Laan et al., 2001; Prause et al., 2003). In addition to CXC chemokines and G-CSF, IL-17A can increase mRNA and protein for the mucins, MUC5AC and MUC5B, in primary human bronchial epithelial cells in vitro (Chen et al., 2003). IL-17A also induces the expression of human beta defensin-2 (Kao et al., 2004) and CCL20 in lung epithelial cells (Huang et al., 2007).

Although the transcription factor NF-κB has been implicated in IL-17R signaling before, the link between IL-17R and activation of mitogen-activated protein kinases (MAPKs) and NF-kB has only recently been elucidated. MAP kinases, in particular p38 and extracellular signal-regulated kinase (ERK), are involved as mediators in IL-17A-induced release of C-X-C chemokines in human bronchial epithelial cells in vitro (Laan et al., 2001). Furthermore, the production of CXCL8 in human synoviocytes is also dependent on the NF-kB and the PI-3 kinase-Akt pathway (Hwang et al., 2004). It has been known for some time that the scaffold protein Traf6 is required for IL-17R signaling, but there are no Traf6-binding sites in the cytoplasmic domain of IL-17RA. Computer-database analysis showed that the members of the IL-17R family contain SEFIR domains, which share homology with Toll-IL-1R domains (Novatchkova et al., 2003). NF-κB activator 1 (Act1), which is an adaptor protein critical for both B cell-activating factor belonging to the TNF family (BAFF) and CD40 signaling, contains SEFIR- and Traf6-binding motifs. Indeed, Act1 binds to the cytoplasmic domain of IL-17RA (Chang et al., 2006b) and is a functional adaptor critical for IL-17RA signaling and the development of EAE and dextran-sodium-sulfate-induced colitis (Qian et al., 2007). TNF-alpha markedly synergizes with IL-17A and IL-17F in inducing G-CSF, CXCL1, and CXCL8 production by epitheilum (Jones and Chan, 2002; McAllister et al., 2005), which is independent of altering IL-17RA expression by TNF-alpha. Gaffen et al. have shown that TNF-alpha can synergize with IL-17A in the nuclear translocation of CCAAT/enhancer-binding protein δ (CEBPδ) (Shen et al., 2006), which explains in part the synergistic affects of IL-17 and TNF-α on CXC chemokine production. Additionally, IL-17A can also augment CXCL1 and G-CSF production by stabilizing the mRNAs encoding these proteins (Cai et al., 1998; Hartupee et al., 2007). In fact, using a HeLa cell reporter assay, Hartupee and colleagues found that the dominant effect of IL-17 was to stabilize the mRNA for these molecules rather than to alter transcription. Moreover, this effect is independent of TNF-α (Hartupee et al., 2007). Thus, there has been much learned regarding IL-17 ligand and receptor signaling; however, the precise mechanisms of IL-17 synergy with TNF-α and IL-22 remains to be determined. Moreover, there is also IL-17-regulated gene expression that occurs in the absence of Act1, and the mechanism underlying this needs to be further defined.

## Role of IL-17 in Autoimmunity: RA, MS-EAE, Psoriasis, and IBD

The role of IL-17 family members in arthritis has recently been extensively reviewed (Lubberts, 2003). Abrogation of IL-17A prior to disease onset attenuates antigen-induced arthritis in mice (Bush et al., 2002; Lubberts et al., 2004). Also, treatment with IL-17A antibodies after the onset of experimental, collagen-induced arthritis decreases joint damage and histologic destruction of cartilage and bone, and it reduces IL-6 in mouse serum as well (Lubberts et al., 2004). Thus, as judged from these studies, IL-17A and IL-17F might contribute to the erosion of cartilage and bone in joint disease. It has also recently been demonstrated that IL-17 regulates germinal-center formation, as well as auto-antibody

production (Hsu et al., 2008). Consistent with these ideas, the loss of the proximal regulator IL-23 is protective in autoimmune arthritis in mice, whereas the loss of IL-12 is associated with exacerbated arthritis as well as an increased number of IL-17A-secreting T lymphocytes (Murphy et al., 2003).

IL-17A is upregulated in central nervous system lesions of patients with multiple sclerosis (MS) (Lock et al., 2002). Moreover, IL-23, rather than IL-12, is more critical for the development of EAE in mice, and neutralization of IL-17 reduces the severity of EAE (Cua et al., 2003). In addition, IL-17A-deficient mice show delayed onset and reduced maximum-severity scores in EAE (Komiyama et al., 2006). Tzartos and collaborators have shown the presence of IL-17-positive perivascular lymphocytes in brain lesions from patients with active MS and a reduction of these cells in quiescent MS (Tzartos et al., 2008). In this study, the investigators observed expression of IL-17 in $CD8^+$ T cells in addition to CD4+ T cells, and expression was also observed in astrocytes and oligodendrocytes.

Teunissen and colleagues described the upregulation of IL-17A in psoriatic skin in 1998 and demonstrated that IL-17A induces intercellular adhesion molecule-1 (ICAM1), IL-6, and IL-8 in human skin keratinocytes (Teunissen et al., 1998). IL-22 also synergizes with IL-17 in the induction of human beta-defensin 2, S100 calcium-binding protein A9 (S100A9, calgranulin B), and additively enhances the expression of S100A7 (psoriasin) and S100A8 (calgranulin A), which have also have been shown to be upregulated in psoriatic skin (Liang et al., 2006). These S100 proteins are involved in the regulation of a number of cellular processes, such as cell cycle progression and differentiation, and the calgranulin proteins have been shown to have both antibacterial and fungicidal activities. Wilson and colleagues studied Th17 cells in human psoriatic skin and found that these cells express IL-23R, IL-17A, IL-17F, IL-26, and CCL20 as well as the transcription factor RORγt (Wilson et al., 2007). These authors also showed upregulation of transcripts for *IL1B*, a critical factor in human Th17 cell differentiation, as well as for *IFNG* (Wilson et al., 2007).

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. Annunziato, studying humans with Crohn's disease, observed the presence of IL-17-producing T cells in the gut, some of which produced IL-17 and IFN-γ (Annunziato et al., 2007). These human IL-17-producing cells also express IL-23R and CCR6 (Annunziato et al., 2007). In a model of TNBS-induced colitis, mice deficient in IL-17RA expression show substantially reduced PMN emigration into the colon, as well as reduced amounts of CXCL2 (Zhang et al., 2006). Blockade of IL-23 is effective in preventing colitis in IL-10-deficient mice, through the inhibition of both IL-17 and IL-6 (Yen et al., 2006). Moreover, using a T cell-independent model of colitis, Uhlig and colleagues showed that IL-23 regulates intestinal inflammation in response to CD40 activation and that this was associated with downregulation of IL-17 in anti-IL-23-treated mice, suggesting the contribution of non-T cell sources of IL-17 in this model (Uhlig et al., 2006).

In conclusion, the IL-17 pathway plays an essential pathological role in many autoimmune diseases. Efficacy, safety, and tolerability studies with AIN457, a monoclonal anti-IL-17 antibody, are underway for Crohn's disease and psoriasis that are resistant to current therapies, and the results of these clinical trials will clearly advance our understanding of the contributions of IL-17 to these diseases. Specifically, it will be important to understand whether anti-IL-17 strategies will have any benefit or enhanced safety compared to anti-

TNF strategies, given the cooperative nature of TNF and IL-17 in the induction of ICAM1 and CXC chemokines in epithelial cells.

## Role of IL-17 in Granulopoiesis and Bone Marrow Recovery after Irradiation

One of the earliest documented activities of IL-17A was the increase of G-CSF in human bone marrow stromal cells, which resulted in the differentiation of CD34+ progenitor into neutrophil progenitors in vitro (Fossiez et al., 1996). Interestingly, unlike IL-17A, IL-17F is unable to support proliferation of granulocyte precursors in vitro (Starnes et al., 2001) despite a similar potency as IL-17A in the recruitment of neutrophils into the lungs of mice (Hurst et al., 2002). Overexpression of IL-17A systemically results in massive extramedullary hematopoiesis in mice, caused by the induction of endogenous G-CSF and stem cell factor (SCF) (Schwarzenberger et al., 2000; Schwarzenberger et al., 1998) IL-17A has also been shown to be critical for the augmented G-CSF amounts, granulopoiesis, and elevated neutrophil counts in peripheral blood of leukocyte-adhesion-molecule-deficient mice (Forlow et al., 2001). This IL-17 production is regulated by IL-23 and phagocytosis of apoptotic neutrophils in the lamina propria (Stark et al., 2005). The source of IL-17A in these mice are a variety of T cell subsets, of which 60% are IL-17A-positive cells being γδgT cells, 25% are NKT-like cells, and 15% are $CD4^+$ T cells (Ley et al., 2006). Although there is a mild reduction of mature neutrophils in IL-17RA-deficient mice, these mice show markedly impaired recovery of their neutrophil counts in response to sublethal irradiation (Tan et al., 2006). Taken together, these data suggest that IL-17 is critical for the regulation of granulopoiesis under physiological stress.

## Role of IL-17 in Host Defense

IL-17RA-deficient mice show defective G-CSF responses, granulopoiesis, and enhanced susceptibility to experimental *K. pneumoniae* pulmonary infection (Ye et al., 2001) However, the enhanced susceptibility to *K. pneumoniae* cannot be fully restored by the restoring of granulpoietic progenitors with exogenous recombinant G-CSF (unpublished observations). Thus, despite treatment with G-CSF, neutrophil recruitment is not restored in the pulmonary tissue compartment, likely due to the defective CXC chemokine production that is seen in these mice (Ye et al., 2001) or in mice treated with IL-17A antibodies (Miyamoto et al., 2003). Similar to IL-17RA-deficient mice, IL-17A-deficient mice are also susceptible to *K. pneumoniae* and show reduced G-CSF and CXCL1 in the lung in response to this infection (Figure 1) (Aujla et al., 2008). Furthermore, endogenous IL-17A, released mainly by $CD4^+$ T lymphocytes, also plays a critical role in the orchestration of the formation of intra-abdominal abscesses and neutrophil accumulation in response to the gram-negative bacteria *Bacteroides fragilis* in vivo (Chung et al., 2003). IL-17RA-deficient mice are also susceptible to *Toxoplasmosis gondii* (Kelly et al., 2005) and *Candida albicans* infection (Huang et al., 2004). However, IL-17RA-deficient mice do not show increased susceptibility to infections with the intracellular pathogens *Mycobacterium tuberculosis* or *Listeria monocytogenes* (Aujla et al., 2008). In the latter case, IL-17RA signaling is dispensable for the IFN-γ-mediated immune responses to *L. monocytogenes.* Although IL-17RA signaling is not required for the primary control of M. *tuberculosis*, enhanced recruitment of Th1 effectors in mice vaccinated with antigens from M. *tuberculosis* is mediated by IL-17A via the regulation of the CXCR3 ligands, MIG, IP-10 and I-TAC, which are critical for the recruitment of Th1 cells to the granuloma (Khader et al., 2007). Thus, these findings suggest that IL-17A and IL-17RA signaling is more critical for extracellular than for intracellular pathogens.

However, the roles of IL-17A and IL-17F in fungal infection remain controversial. It has recently been shown that IL-17A negatively regulates Th1 responses to *A. fumigatus* and *C. albicans* and permits more extensive growth of fungi in vivo (Zelante et al., 2007).

Moreover, IL-17A inhibits antifungal activity in vitro. However, these studies were performed with commercial preparations of IL-17A produced in *E. coli*, which have different glycosylation patterns from eukaryotically produced IL-17A and also contain trace amounts of LPS. Therefore, it would be important to confirm that these effects are truly IL-17RA dependent and to ascertain whether the results can be extrapolated to human neutrophils. In a follow-up paper, Romani and colleagues demonstrated that the increased pathology induced by *A. fumigatus* infection in mice lacking functional NADPH oxidase led to defective function of indoleamine 2,3-dioxygenase (IDO), which resulted in increased IL-23 expression as well as in augmented recruitment of Vγ1 γδ T cells expressing IL-17 (Romani et al., 2008). Neutralization of IL-17 in NADPH-oxidase-deficient mice reduces the enhanced pathology in response to *A. fumigatus* challenge (Romani et al., 2008). Both IL-23 and IL-17 have also been found to be elevated in cystic fibrosis (CF) patients who are colonized with mucoid strains of *P. aeruginosa* (Dubin and Kolls, 2007). Modeling chronic *P. aeruginosa* infection with bacteria containing agarose beads demonstrates that deficiency of IL-23 improves the immunopathology induced by chronic *P. aeruginosa* infection. In this model, IL-23 is not required to control bacterial growth and the decrease in inflammation is associated with significantly reduced expression of IL-17. Thus, in certain infections, IL-23 and IL-17 might contribute to tissue pathology as opposed to host defense. Moreover, the contributions of IL-17F in both host defense and immunopathology need to be determined.

## IL-21

The discovery of IL-21 receptor (IL-21R) precedes the discovery of IL-21. IL-21R was discovered as a type I cytokine receptor (Ozaki et al., 2000; Parrish-Novak et al., 2000), which was originally termed “novel interleukin receptor” (NILR) (Ozaki et al., 2000). It is most similar to the IL-2 receptor β chain and is located on human chromosome 16, immediately adjacent to the gene encoding IL-4 receptor α chain (Ozaki et al., 2000; Parrish-Novak et al., 2000). The ligand for IL-21R, IL-21, was subsequently discovered with a functional ligand-screening approach based on expression of the receptor (Parrish-Novak et al., 2000). IL-21 is most similar to IL-2, IL-4, and IL-15 (Parrish-Novak et al., 2000), which are cytokines with receptors that contain the common cytokine-receptor γ chain ($\gamma_c$). Correspondingly, the functional IL-21 receptor for IL-21 consists of IL-21R and $\gamma_c$ (Asao et al., 2001; Habib et al., 2002). Depending on the cell type, signaling through the IL-21R and $\gamma_c$ receptor complex can activate the downstream targets, including Janus activated kinase 1 (Jak1), Jak3, signal transducers and activators of transcription 1 (Stat1), Stat3, Stat4, and Stat5 (Mehta et al., 2004).

## Role of IL-21 in Lymphocyte Regulation

IL-21 is produced mainly by $CD4^+$ T cells (Parrish-Novak et al., 2000), as well as by NKT cells (Coquet et al., 2007). Since its discovery, IL-21 has been proposed to be an effector cytokine that is preferentially produced by various T helper cell subsets, including Th2 cells (Wurster et al., 2002), and T follicular helper ($T_{FH}$) cells, a population of follicular $CD4^+$ T cells that function in B cell help but do not have a Th1 or Th2 cell phenotype (Bryant et al., 2007; Chtanova et al., 2004). IL-21 also promotes Th1 responses (Monteleone et al., 2005; Strengell et al., 2002). Most recently, however, several groups simultaneously identified that IL-21 was also produced by Th17 cells and exerted critical functions in Th17 cell development (Korn et al., 2007; Nurieva et al., 2007; Zhou et al., 2007).

IL-21R is expressed on T cells, B cells, NK cells, dendritic cells (DCs), macrophages, and epithelial cells (Brandt et al., 2003a; Caruso et al., 2007; Distler et al., 2005; Jin et al., 2004; Ozaki et al., 2000; Parrish-Novak et al., 2000), indicating a broad range of actions for IL-21. IL-21 is indispensable in the regulation of various immune responses. Both the Th1 cytokine IFN-γ and Th2 cytokine IL-4 have important functions in the promotion of their own

expression from Th1 and Th2 cells, respectively. Similarly, IL-21 functions in an autocrine loop to amplify the Th17 cell response and induce its own expression (Figure 2) (Korn et al., 2007; Nurieva et al., 2007; Zhou et al., 2007). IL-21, like IL-6, can favor the generation of Th17 cells over Treg cells. For both IL-21 and IL-6, this switch seems to be mediated by STAT3 and RORγt (Korn et al., 2007; Nurieva et al., 2007; Zhou et al., 2007).

In addition, IL-21 has a much broader function beyond the regulation of Th17 cells. IL-21 can promote both humoral responses and cellular immunity, which are traditionally considered to be mediated by Th2 cytokines, such as IL-4, and Th1 cytokines, such as IFN-γ, respectively. First, IL-21 plays a critical role in B cell function (Figure 2). Although IL-21R deficient mice show no defects in B cell subsets and development, they have a reduced amount of serum IgG1 and an increased amount of IgE (Ozaki et al., 2002). Furthermore, immunization of these mice with T cell-dependent antigens results in lower levels of antigen-specific IgG1 but substantially higher amounts of IgE (Ozaki et al., 2002). Consistently, administration of IL-21 to wildtype mice at the time of immunization can lead to decreased antigen-specific IgE titers (Suto et al., 2002). IL-21 can serve as a complex regulator of B cell maturation and terminal differentiation by inducting the expression of transcription factors, such as Blimp-1 and Bcl-6 (Ozaki et al., 2004).

Second, IL-21 can also augment cellular immunity by promoting the functions of Th1 cells, $CD8^+$ cells, and NK cells. IL-21 stimulates IFN-γ production from both Th1 cells and NK cells (Monteleone et al., 2005; Strengell et al., 2002). Moreover, IL-21 synergizes with IL-15 in regulation of the proliferation and activation of both naïve and memory $CD8^+$ T cells (Kasaian et al., 2002; Zeng et al., 2005). In addition, IL-21 also modulates the functional development of NK cells. IL-21 was originally shown to enhance in vitro generation of NK cells from human bone-marrow progenitors (Parrish-Novak et al., 2000). Studies with human cord-blood precursors confirm that IL-21 is capable of inducing an accelerated NK cell maturation and acquisition of a mature killer Immunoglobin (Ig)-like receptor (KIR) repertoire when added to cultures of $CD34^+$ $Lin^-$ cells supplemented with IL-15, Flt3-L (Fetal liver tyrosine kinases 3-ligand), and SCF (stem cell factor) (Sivori et al., 2003). The IFN-γ production by NK cells is also synergistically upregulated in the presence of IL-21 and IL-15 (Habib et al., 2002). Interestingly, IL-21R-deficient mice have normal numbers of fully functional NK cells (Kasaian et al., 2002; Ozaki et al., 2002), indicating that IL-21 is not required for the earliest commitment of NK cell lineage. But once committed immature NK cells are generated, IL-21 has a bi-phasic effect on their growth: Low doses of IL-21 increase the proliferative responses of these cells, whereas high doses of IL-21 inhibit proliferation (Toomey et al., 2003). IL-21 also has effects on mature NK cells, including effects on both proliferation and survival as well as on NK cell-specific surface receptor (Brady et al., 2004; Gays et al., 2005). Finally, IL-21 can induce an inhibitory DC phenotype (Brandt et al., 2003a; Brandt et al., 2003b) while augmenting proliferation and/or differentiation of monocyte-macrophage and granulocyte lineages (Wang et al., 2003).

In conclusion, IL-21 has clearly pleiotropic functions on various immune cells. Its role on nonimmune cells, however, also cannot be ignored. Recent studies have shown that T cell-derived IL-21 can act on intestinal fibroblast and epithelia cells to synthesize matrix metalloproteinases (MMPs), which then mediate mucosal degradation (Caruso et al., 2007; Monteleone et al., 2006).

## Role of IL-21 in Inflammation

In view of its role in controlling a complex range of immune components through either positive or negative regulation, the IL-21 pathway might also be involved in human autoimmune diseases. Preclinical and clinical data suggest a pathological role for IL-21 in many human diseases, including human systemic lupus erythematosus (SLE), MS, type I

diabetes, and IBD. First, polymorphisms of IL-21 have been revealed to genetically associate with human SLE (Sawalha et al., 2008). In the BXSB.B6-*Yaa*$^{+}$ mouse model of SLE, increased expression of IL-21 has been detected (Ozaki et al., 2004), consistent with the increased Ig amounts in the mice and the role of IL-21 in B cells. A ring-type ubiquitin ligase, roquin, has been identified as playing an important role in the repression of inducible costimulator (ICOS) and IL-21. A mutation disrupting roquin function not only increases the expression of ICOS and IL-21 but also results in the development of lupus-like autoimmune phenotypes in mice (Vinuesa et al., 2005). Moreover, blocking of the IL-21 pathway ameliorates the autoimmune symptoms in a mouse model of SLE (Herber et al., 2007). Second, in the nonobese diabetic (NOD) mouse model, one of the genetic loci that are associated with disease is the insulin-dependent diabetes susceptibility 3 (*Idd3*) locus that contains the genes encoding both IL-21 and IL-2 (Denny et al., 1997). NOD mice have increased expression of IL-21, and it has been suggested that this promotes the homeostatic proliferation of an autoreactive CD8$^{+}$ T cell population (King et al., 2004). Third, in the EAE model, IL-21 administration before induction of EAE enhances the inflammatory influx into the central nervous system as well as the severity of EAE, whereas no such effects are observed when IL-21 is administered after EAE progresses (Vollmer et al., 2005). Although in this study the ability of IL-21 to exacerbate disease is attributed to IL-21-activated NK cells, recent studies have indicated a role for IL-21 in the induction and expansion of Th17 cells in this EAE model (Korn et al., 2007; Nurieva et al., 2007). Finally, IL-21 is involved in the crosstalk between nonimmune cells and immune cells in the gut, as we discussed, suggesting that T cell-derived IL-21 could be associated with gastric inflammation. For example, in celiac disease, genetic studies have identified risk variants in the region harboring the *IL21* gene (van Heel et al., 2007), and enhanced IL-21 mRNA and protein expression are seen in duodenal samples from untreated celiac disease patients (Fina et al., 2007). Furthermore, enhanced IL-21 expression is also detected in biopsies from patients suffering from Crohn's diseases (Monteleone et al., 2005) and *Helicobacter pylori* infection (Caruso et al., 2007). In summary, these studies support an essential role of IL-21 in the pathogenesis of many autoimmune diseases.

## IL-22

IL-22 is one of the IL-10-family cytokines, which also include IL-10, IL-19, IL-20, IL-24, and IL-26, as well as more distally related IL-28 and IL-29. IL-22 was first identified as an IL-10-related T cell-derived inducible factor (IL-TIF) from a lymphoma cell line treated with IL-9 by use of a cDNA subtractive technique (Dumoutier et al., 2000a). IL-22R and IL-10R2 were soon identified as the heterodimeric receptor complex for the function of IL-22 (Kotenko et al., 2001a; Xie et al., 2000). Later, IL-22R was also found to pair with the IL-20R2 chain to form a different receptor complex, which together with IL-20R1 and IL-20R2 served as the functional receptors for IL-20 and IL-24 signaling (Dumoutier et al., 2001a; Wang et al., 2002). IL-22R, IL-20R1, and IL-20R2 all belong to the class II cytokine-receptor family (Pestka et al., 2004). Genome-wide searching for novel members of this receptor family lead to the discovery of a soluble receptor: IL-22BP, or IL-22RA2 ((Dumoutier et al., 2001b; Kotenko et al., 2001b; Xu et al., 2001). IL-22BP shares substantial sequence homology with IL-10R-family receptors, especially IL-22R, but it lacks the hydrophobic transmembrane domain. In vitro, IL-22BP binds to IL-22 and neutralizes its biological activities.

The tertiary structure of IL-22 is different from that of IL-10 despite their sequence homology. Unlike IL-10, IL-22 does not form an intimate intertwined dimer, and it might be able to interact with its receptor as a monomer (Nagem et al., 2002). Upon binding to the receptor complex, IL-22 induces the phosphorylation of tyrosine kinases Jak1 and Tyk2, which initiates the signaling cascade through activation of Stat3 and, to a lesser extent, Stat1

and Stat5 (Dumoutier et al., 2000a; Lejeune et al., 2002; Xie et al., 2000). In addition, IL-22 has also been reported to activate three major MAP kinase pathways: the MEK-ERK-RSK pathway, the JNK-SAPK pathway, and the p38 pathway (Lejeune et al., 2002).

## Cellular Sources and Regulation of IL-22

Early studies suggested that leukocytes, especially T cells, were the likely cellular sources of IL-22 (Dumoutier et al., 2000a; Xie et al., 2000). RT-PCR-based analysis reveals that upregulation of IL-22 transcripts are detected in anti-CD3-activated T cells and IL-2- or IL-12-stimulated NK cells (Wolk et al., 2002). IL-22 production by activated memory $CD4^+$ T cells is much higher than that from activated naïve T cells. There is also greater induction of IL-22 under Th1 cell differentiation conditions than there is under Th2 cell differentiation conditions. The emergence of the Th17 cell subset prompted several groups to examine the production of IL-22 by these cells (Chung et al., 2006; Liang et al., 2006; Zheng et al., 2007). Although Th1 cells make more IL-22 as compared to Th2 cells or undifferentiated T cells, Th17 cells are clearly the dominant IL-22 producers by far, as demonstrated at both the mRNA and protein levels. These data unequivocally establish that IL-22 is another effector cytokine produced by Th17 cells.

The coexpression of IL-17 and IL-22 in Th17 cells suggests that the pathways that regulate these two cytokines might be very similar. Detailed analysis, however, demonstrates some differences between the inductions of these two cytokines (Zheng et al., 2007). First, although IL-23 is insufficient to induce de novo IL-17 production from naïve $CD4^+$ T cells, IL-23 alone promotes IL-22 production from many different immune cell types. Second, in contrast to the induction of IL-17, the induction of IL-22 does not require TGF-β. IL-6 alone is sufficient for the induction of IL-22 from naïve $CD4^+$ T cells. The molecular basis of these differences is currently unclear. Nonetheless, the differential regulation of these two cytokines could have important implications for their in vivo functions during different disease processes. Although both IL-6 and IL-23 stimulate IL-22 production in vitro (Zheng et al., 2007), only IL-23 seems to be indispensable in vivo for IL-22 induction under several infectious or autoimmune-disease conditions (Aujla et al., 2008; Zheng et al., 2008). IL-6 is not essential for IL-22 induction, at least in ConA-induced hepatitis and *C. rodentium* infection models (Zenewicz et al., 2007; Zheng et al., 2008). It is, however, required for maximal IL-17 production during *C. rodentium* infection in the colon (Zheng et al., 2008).

IL-23 also induces IL-22 production from $CD8^+$ T cells and γδ T cells in addition to that from $CD4^+$ T cells (Zheng et al., 2007). Besides cytokines, a cell-surface molecule called nectin-like protein 2 (Ncl2) is expressed on a subset of DCs and promotes IL-22 production from $CD8^+$ T cells through its interaction with an immunoglobulin-superfamily transmembrane protein, CRTAM (Galibert et al., 2005). Strikingly, $CD4^+$ T cells from CRTAM-deficient mice have compromised IFN-γ, IL-22, and IL-17 production, as well as defects in cell polarity, during activation and differentiation (Yeh et al., 2008). Furthermore, although LPS is not able to stimulate IL-22 production in monocytes (Wolk et al., 2002), IL-23 alone can stimulate IL-22 secretion in both monocytes and $CD11c^+$ DCs (Zheng et al., 2007; Zheng et al., 2008). Importantly, in vivo studies elucidated that IL-22, produced both from T cells and elsewhere, was essential for host defense against various infections (Aujla et al., 2008; Zheng et al., 2008).

## Regulation of the Biology of Epithelial Cells by IL-22

Soon after the discovery of IL-22, it was realized that cells with nonhematopoietic origin were probably targeted by IL-22. Whereas the IL-10R2 chain is ubiquitously expressed, the expression of IL-22R is restricted to tissue-resident cells, especially those of epithelial origin (Aggarwal et al., 2001; Dumoutier et al., 2000b). To date, the expression of IL-22R has not

been reported in immune cells, and immune cells seem not to be directly responsive to IL-22 stimulation (Lecart et al., 2002; Wolk et al., 2002; Wolk et al., 2004; Zheng et al., 2008). On the contrary, IL-22 elicited very strong responses from many epithelial cells or cell lines, including acinar cells, hepatocytes, keratinocytes, and colon epithelial cells (Aggarwal et al., 2001; Andoh et al., 2005; Dumoutier et al., 2000b). Data from in vitro studies with various primary cells and cell lines implicate the potential roles of IL-22 in host defense, inflammation, and tissue repair (Boniface et al., 2005; Sa et al., 2007; Wolk et al., 2004). First, IL-22 induces proinflammatory responses, such as the production of cytokines, chemokines, and acute-phase proteins, from many cell types. Second, IL-22 drives the production of many antimicrobial peptides, including β-defensins, S100-family proteins, and regenerating-gene (Reg)-family proteins. Genome-wide searching of potential downstream targets further uncovered a large group of genes involved in tissue-repair and wound-healing responses from keratinocytes when treated with IL-22 (Sa et al., 2007; Wolk et al., 2006). Moreover, IL-22 also stimulates proliferation, abnormal differentiation, and migration of various epithelial cells in vitro (Boniface et al., 2005; Brand et al., 2006; Sa et al., 2007). Together, these data strongly support a role of IL-22 in host defense and epithelial-barrier function.

## Role of IL-22 in Autoimmunity

The first hint of a pathological role of IL-22 in autoimmune diseases comes from the study of its related family member, IL-20. Transgenic mouse lines overexpressing IL-20 under the control of several different promoters all developed a skin phenotype reminiscent of that of psoriatic skin, supporting a role of IL-20 in the pathogenesis of psoriasis (Blumberg et al., 2001). IL-20 also signals through IL-22R and IL-20R2 complexes, as well as through IL-20R1 and IL-20R2 (Dumoutier et al., 2001a). Furthermore, IL-22 is upregulated in psoriatic skin, suggesting a similar role in the pathogenesis of psoriasis for IL-22 (Wolk et al., 2006). In vitro, IL-22 induces many psoriatic features from cultured reconstituted human epidermis, further corroborating this premise (Boniface et al., 2005). Recently, a critical role of IL-23 in the pathogenesis of psoriasis was indicated on the basis of both genetic-association study and human clinical data (Cargill et al., 2007; Kauffman et al., 2004; Krueger et al., 2007; Lee et al., 2004). IL-23 primarily targets immune cells (Kastelein et al., 2007). IL-22, therefore, might be an obvious downstream factor of IL-23 that mediates the crosstalk between infiltrating immune cells, especially T cells, and keratinocytes in psoriatic skin. Injection of IL-23 into a mouse ear causes an inflammatory skin phenotype, characterized as leukocyte infiltration and epidermal acanthosis (Zheng et al., 2007). The infiltrating $CD4^+$ T cells display a Th17 cell phenotype with the expression of both IL-17 and IL-22. These pathological features induced by IL-23 are dramatically diminished in IL-22-deficient mice. The reduction of the acanthosis observed in the ear after IL-23 administration is accompanied by a decrease of Stat3 activation in epidermal keratinocytes as well as reduced neutrophil infiltration (Zheng et al., 2007). Consistent with these observations, administration of an IL-22-specific antibody ameliorates the inflammatory skin disease in a murine model of psoriasis (Ma et al., 2008). In conclusion, these data support a potential pathological role of IL-22 in psoriasis.

Expression of IL-22 is also augmented in many other autoimmune diseases. The upregulation of IL-22 is detected both in Crohn's diseases (CD) and ulcerative colitis, as well as in preclinical mouse IBD models (Andoh et al., 2005; Brand et al., 2006; te Velde et al., 2007). In CD, the IL-22 serum amount correlates with disease activity (Schmechel et al., 2008). IL-22 induces proinflammatory cytokines, as well as proliferation and migration of several intestine epithelial cell lines (Andoh et al., 2005; Brand et al., 2006). In vivo, IL-22 can stimulate the production of LPS-binding protein, which is also elevated in the blood of CD patients (Wolk et al., 2007). Recent genetic studies identified the association of the

IL-23R pathway with the pathogenesis of CD. Interestingly, the IL-23R gene variants seem to influence the serum amount of IL-22 (Schmechel et al., 2008). IL-22 is higher in the serum of carriers with IL-23R alleles that increase CD risk than in that of carriers with IL-23R alleles that decrease CD risk. However, as we discuss below, given the important role of IL-22 in the control of bacterial infections in the gastrointestinal tract, whether IL-22 has a protective or pathogenic role in IBD needs to be further elucidated. A recent study demonstrates that, at least in some preclinical models of IBD, IL-22 elicits a protective rather than pathological role (Sugimoto et al., 2008).

Elevated IL-22 is also detected in synovial tissues of rheumatoid arthritis (RA) patients, and IL-22 promotes the proliferation and chemokine production of synovial fibroblasts (Ikeuchi et al., 2005). The function of IL-22 in preclinical RA models has not been reported. Similarly, the functional role of IL-22 has not been examined in preclinical asthma models. IL-22, however, is present in the bronchoalveolar lavage (BAL) fluid samples of normal individuals and is reduced in BAL fluid samples from patients with acute respiratory-distress syndrome and sarcoidosis (Whittington et al., 2004). In mice, direct administration of IL-17, but not of IL-22, into the airway increases the recruitment of neutrophils and the expression of chemokines (Liang et al., 2007). On the other hand, IL-22 production is elevated in the lymphoid tissues from cystic fibrosis patients, and IL-22 plays an essential role, as discussed below, in host control of the Gram-negative pulmonary pathogen *Klebsiella pneumoniae* (Aujla et al., 2008). These studies suggest that there might be a role for IL-22 in asthma. A recent study shows that IL-17- and IL-22-expressing human Th17 cells cross the blood-brain barrier efficiently, and both IL-17 and IL-22 promote the disruption of the blood-brain barrier in vitro and in vivo (Kebir et al., 2007). In preclinical EAE, IL-22 is dispensable, despite the fact that IL-22 is a direct downstream target of IL-23 and that IL-23 has essential pathogenic functions in this model (Kreymborg et al., 2007).

In addition to its proinflammatory role, IL-22 also induces tissue-repair and wound-healing responses from tissues, implying that it might prevent tissue damage under certain inflammatory conditions. This postulation was supported by studies in the ConA-induced hepatitis model. IL-22 is substantially elevated after ConA injection. IL-22 protects the liver injury by enhancing the growth and survival of hepatocytes (Radaeva et al., 2004).

Studies with both IL-22- and IL-17-deficient mice further point to a protective function of IL-22, but not IL-17, produced by Th17 cells (Zenewicz et al., 2007). Consistent with these results, IL-22 has also been shown to elicit a protective function in a rat model of experimental autoimmune myocarditis (Chang et al., 2006a). In conclusion, IL-22 can exert both pathogenic and protective functions in autoimmune diseases, depending on the specific situations and target cells.

## Role of IL-22 in Infections

The induction of many antimicrobial peptides from various cell types leads to the speculation that IL-22 might participate in host defense for pathogens (Wolk et al., 2004). In individuals who are resistant to HIV infection, IL-22 production by activated T cells is substantially higher (Misse et al., 2007). IL-22 might be protective through induction of the acute-phase protein SAA in these individuals. A genetic-association study identifies IL-22 as a candidate in the control of mortality during Theiler's virus-induced encephalomyelitis (Levillayer et al., 2007). These two studies support the involvement of IL-22 in the control of viral infections. Additional studies are needed to confirm these hypotheses and also to provide downstream mechanistic explanations. Interestingly, in a polymicrobial peritonitis model, blocking of IL-22 by mouse IL-22BP fusion protein reduces bacterial load and organ damage, suggesting that IL-22 contributes to bacterial spread and organ failure (Weber et al., 2007). This observation currently has not been confirmed, however, with high-affinity

neutralizing antibody or in IL-22-deficient mice. Given the role of IL-22 in liver inflammation, IL-22-deficient mice have also been tested with the infection of *Listeria monocytogenes*, a Gram-positive intracellular bacterium (Zenewicz et al., 2007). Both innate and adaptive immune responses against *L. monocytogenes* are normal in the absence of IL-22. This result is not surprising, given that $CD8^+$ T cells and the Th1 response play more important roles in the control of intracellular pathogens.

The expression of the IL-22 receptor on various epithelial cells suggests that IL-22 could be involved in mucosal immunity during infections. As mentioned above, IL-17 and IL-22 can synergistically or additively increase antimicrobial proteins in the skin keratinocytes (Liang et al., 2006). Similarly, primary human bronchial epithelial cells express IL-17RA (McAllister et al., 2005), IL-17RC (Kuestner et al., 2007), and IL-22R (Aujla et al., 2008). Stimulation of these cells with IL-22 and IL-17A induces the expression of several host-defense genes, including those encoding human beta defensin -2 (*DEFB4*), *IL19*, *CSF3*, *IL-1F9*, *S100A7* and *S100A12, DUOX2*, *CXCL1, CXCL5,* and CXCL*9*, as well as *CCL3* (Figure 1). IL-22 also increases the clonogenic potential of human bronchial epithelial cells and enhances wound repair in these cells (Figure 1) (Aujla et al., 2008).

Th17 cells are enriched at the mucosal sites of infection in two pathogenic challenge models (Happel et al., 2005; Mangan et al., 2006). In the first model, infection of *K. pneumoniae* in the lung augments the expression of both IL-23 and IL-17, and both IL-23 and IL-17 are necessary for the host to elicit full immune responses to the infection (Happel et al., 2005). IL-17R-deficient mice have reduced survival rates and fail to augment G-CSF responses, which leads to defective granulopoiesis. In the second model, *Citrobacter rodentium* inoculation in the mouse colon results in an increased number of $CD4^+$ T cells that produce IL-17. IL-23 is essential for host defense during the early phase of infection, given that all IL-23-deficient mice succumb during the second week of the infection whereas all wild-type mice survive the infection (Mangan et al., 2006).

Is there a role of IL-22 in these two models? IL-22 is quickly upregulated in both models (Aujla et al., 2008; Zheng et al., 2008). Most importantly, disruption of the IL-22 pathway by use of either neutralizing antibodies or IL-22-deficient mice completely compromises the ability of the host to control both infections, indicating an indispensable role of IL-22 in mucosal immunity (Figure 1 and Figure 2). There are some similarities of the biology of IL-22 in both models. In both models, IL-23 is absolutely essential for IL-22 induction during the infection. IL-22 restores mucosal immunity against *K. pneumoniae* in IL-23p19-deficient mice (Aujla et al., 2008). Furthermore, in both models IL-22 targets epithelial cells, although from different origins, to elicit host immunity.

On the other hand, there are also differences in these models. In the *K. pneumonia* infection model, IL-22 is induced in the lung with kinetics similar to those of IL-17A, and both cytokines are important for host defense (Aujla et al., 2008). As opposed to IL-17A deficiency, neutralization of IL-22 is not associated with diminished G-CSF or CXCL1. During *C. rodentium* infection in the colon, IL-22 peaks around day 4 after bacterial inoculation. IL-17, however, reaches its maximum expression on day 12, and the IL-17 pathway is dispensable during the early phase of *C. rodentium* infection (Zheng et al., 2008). Strikingly, the cellular sources of IL-22 in both models are also different. T cells, presumably Th17 cells, are likely cellular sources of IL-22 and IL-17 in the lung during *K. pneumonia* challenge (Aujla et al., 2008). On the contrary, T cells, as well as B cells, are not necessary for IL-22 induction in the colon during *C. rodentium* infection (Zheng et al., 2008). Innate immune cells, such as DCs, are accountable for the most of the IL-22 production during the early phase of infection. Finally, the downstream defense mechanisms induced by IL-22 are also distinct from each other in these models. During *K. pneumonia*

infection in the lung, IL-22 synergizes with IL-17 to induce repair in lung epithelium and antimicrobial responses, including the production of proinflammatory cytokines and chemokines, as well as production of Lipocalin from lung epithelial cells. Lipocalin-2 is required for lung-epithelial killing of *K. pneumoniae* in vitro (Aujla et al., 2008) and killing of *E. coli* in vivo (Flo et al., 2004) On the other hand, Reg-family antimicrobial peptides, such as RegIIIγ and RegIIIβ, are among the key downstream anti-infectious agents that are induced by IL-22 from colon epithelial cells (Zheng et al., 2008). RegIIIγ and RegIIIβ can directly kill Gram-positive bacteria and induce aggregation of *E.coli* in vitro, respectively (Cash et al., 2006; Iovanna et al., 1991). Despite these differences, these studies conclusively support the essential role of IL-22 in mucosal immunity for the control of various infections, especially extracellular bacterial infections.

These results also have relevance to human infections. The IL-22 pathway is intact in both human lung and colon epithelia. Although patients with cystic fibrosis have large numbers of *P. aeruginosa* in the lung, bacteremia with *P. aeruginosa* is rare. These patients have significantly elevated basal IL-22 responses and stimulated IL-22 responses in their hilar lymph, and this might well be required for the mucosal immunity that prevents bacteremia in these patients (Aujla et al., 2008).

## Conclusions

The discovery of the Th17 cell subset and the biological functions of its effector cytokines substantially advanced our understanding of the roles of $CD4^+$ T cells in adaptive immunity, as we discussed above. Despite the recent progress, however, many issues remain to be addressed. First, conditions promoting human Th17 cell differentiation are not universally established. Second, how IL-6, TGF-β, IL-23, and other factors control Th17 cells in vivo under various inflammatory conditions is still largely unclear. Finally, Th17 cells and their effector cytokines have both pathological and protective roles during inflammation. The balances of these functions are not well understood during the processes of many autoimmune and infectious diseases. Answers on these questions are important for the development of future therapeutic strategies to treat various autoimmune and infectious diseases. At present, therapies that modulate the Th17 cell pathway are being tested in the clinic for the treatment autoimmune diseases. For example, a p40 antibody has been tested in psoriasis and IBD, as has an IL-6R antibody in RA. The effector cytokines of Th17 cells, such as IL-17, IL-21, and IL-22, are potential future therapeutic targets. A challenge is to figure out the balance between their beneficial and pathological roles given the complicated functions of these cytokines in inflammation.

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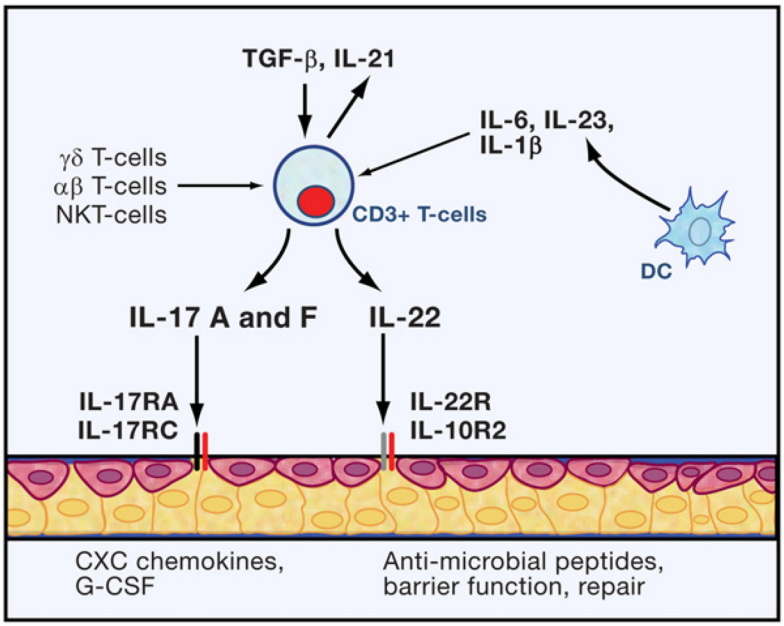


**Figure 1. Functions of IL-17 and IL-22 during*K. pneumonia* Infection in the Lung**

IL-17 and IL-22 are induced rapidly in experimental bacterial pneumonia and are produced by several T cell populations in the lung, including γδ-T cells and NKT cells as well as effector memory αβ $CD4^+$ T cells. IL-17 signaling regulates granulopoiesis, through the regulation of G-CSF, as well as neutrophil recruitment, via the regulation of CXC chemokines by epithelial cells. IL-22 and IL-17 induce antiamicrobial peptides from the same target cells, and IL-22 can augment epithelial repair. This cooperative induction of neutrophil recruitment and this antimicrobial-peptide production augment epithelial-barrier function and are critical for mucosal host defense against Gram-negative bacterial pneumonia.

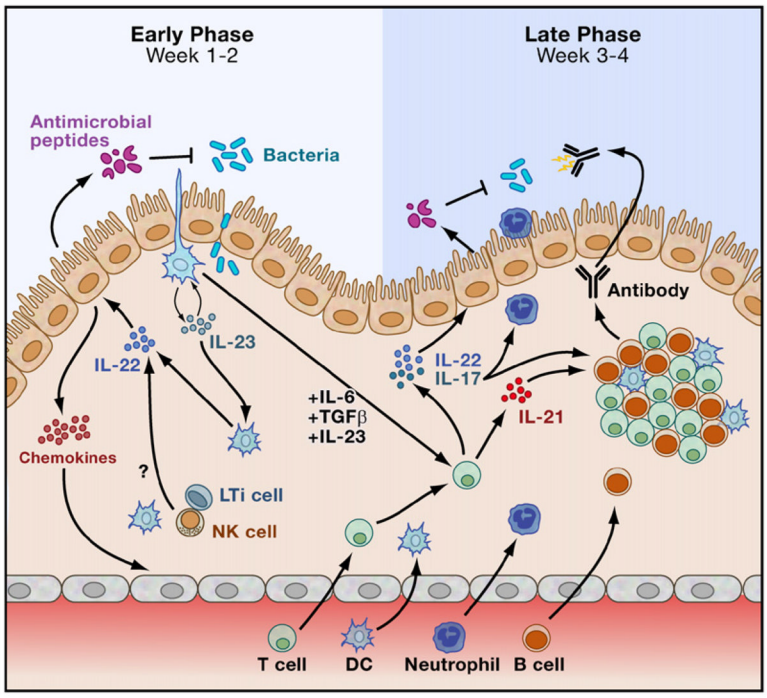


**Figure 2. Potential Functions of IL-17, IL-22, and IL-21 during*C. rodentium* Infection in the Colon**

During the early phase of *C. rodentium* infection, the invasion of attaching-effacing bacteria results in the induction of IL-23. IL-23 promotes early IL-22 production in innate immune cells, especially DCs. IL-22 directly acts on colon epithelial cells to induce antimicrobial peptides, such as Reg-family proteins, and chemokines that recruit leukocytes to the site of infection. IL-22 plays an indispensable role during the early phase of infection in protection of the integrity of the colon epithelial layer and prevention of systemic spreading of the bacteria. In the late phase of infection, the adaptive immunity is essential for the final eradication of the bacteria from the colon. Th17 cells and the effector cytokines IL-17 and IL-21 might have important functions during this phase. Both IL-17 and IL-21 can help the formation of lymph aggregates in the colon and promote the production of bacterial-specific antibodies, which kill and eliminate bacteria.