The Roles of IL-17A and IL-17F in Mucosal Infection and Allergy

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Abstract T_H17 cells are a subset of $CD4^+$ helper T cells that produce IL-17A, IL-17F, IL-9, IL-21, and IL-22. They play an important role in promoting allergic and auto-immune responses as well as in protecting hosts against pathogens. Because IL-17A and IL-17F have the highest homology among IL-17 family members and bind the same IL-17RA and IL-17RC receptor complex, it is suggested that these two cytokines have similar functions. However, accumulating evidence suggests that these cytokines have overlapping yet distinct roles in the immune system. In this review, we introduce how IL-17A and IL-17F are involved in inflammatory immune responses and host defense mechanisms and discuss their relationship with other cytokines in the development of inflammatory and infectious diseases.

1 IL-17A and IL-17F

The IL-17A gene, originally called CTLA-8 (cytotoxic T lymphocyte associated antigen-8) gene, was first cloned from a murine cytotoxic T lymphocyte (CTL) hybridoma cDNA library. Murine IL-17A is a 21-kDa glycoprotein with 147 amino acids and 63% amino acid homology with human IL-17A (155 amino acids). Recently, five additional related cytokines were identified (IL-17B, IL-17C, IL-17D, IL-17E also called IL-25, and IL-17F) with 16–50% amino acid identity with IL-17A (Aggarwal and Gurney 2002; Kolls and Linden 2004). Among these IL-17 family members, IL-17F has the highest amino acid sequence homology to IL-17A. The *Il17f* gene is located close to the *Il17a* gene in both humans and mice.

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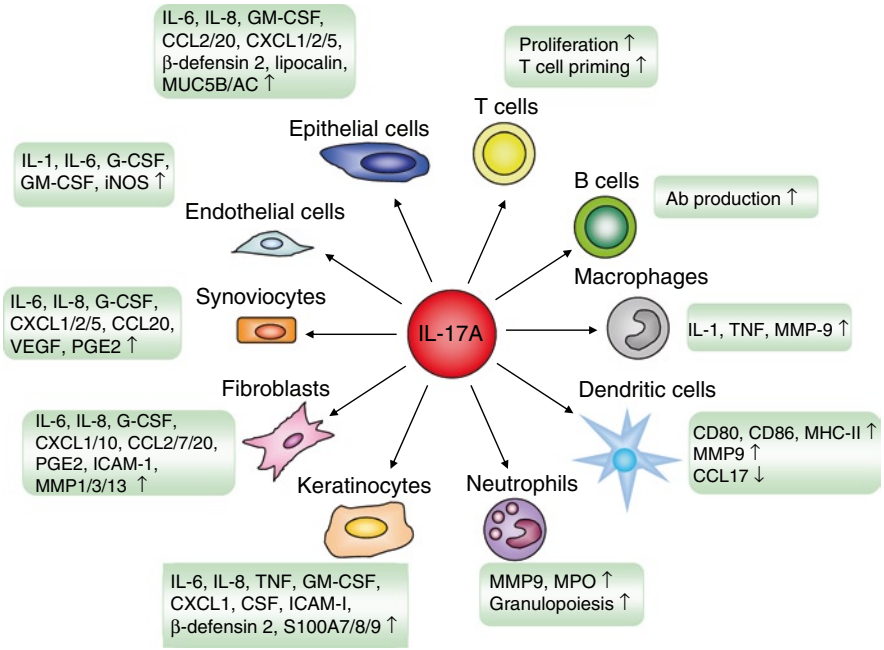

Fig. 1 Pleiotropic effects of IL-17A on multiple target cells

Both IL-17A and IL-17F induce the production of antimicrobial peptides (defensins and S100 proteins), cytokines (IL-6, G-CSF, and GM-CSF), chemokines (CXCL1, CXCL5, IL-8, CCL2, and CCL7), and matrix metalloproteinases (MMP1, MMP3, and MMP13) from fibroblasts, endothelial cells, and epithelial cells (Fig. 1). IL-17A induces intercellular cell adhesion molecule 1 (ICAM-1) in keratinocytes, IL-1 and TNF in macrophages, and iNOS and cyclooxygenase-2 (COX-2) in chondrocytes. IL-17A also promotes SCF and G-CSF-mediated granulopoiesis. Overexpression of IL-17A and IL-17F in the lungs of mice leads to increased pro-inflammatory cytokine and chemokine expression, causing inflammation associated with neutrophil infiltration (Oda et al. 2005; Park et al. 2005; Yang et al. 2008a). These observations suggest that these cytokines have similar biological functions. Furthermore, IL-17A and IL-17F are secreted as both homodimers and heterodimers. The IL-17A-IL-17F heterodimer is more potent than IL-17F, but less potent than IL-17A in inducing chemokine expression (Liang et al. 2007; Wright et al. 2007).

The IL-17 receptor family members (IL-17RA–IL-17RE) have also been identified (Gaffen 2009). Both IL-17A and IL-17F bind the same receptor complexes, IL-17RA and IL-17RC (Zheng et al. 2008), as both IL-17A and IL-17F failed to induce chemokine expression in either *Il17ra*$^{-/-}$ or *Il17rc*$^{-/-}$ cells (Yang et al. 2008a; Zheng et al. 2008). The expression of IL-17RA and IL-17RC is quite different; IL-17RA is highly expressed in lymphoid tissues, whereas IL-17RC is mainly

expressed in non-hematopoietic tissues (Yao et al. 1995; Kuestner et al. 2007; Ishigame et al. 2009), suggesting that these receptors have different functions. Because the binding affinity of IL-17F to IL-17RA is much lower than that of IL-17A (Hymowitz et al. 2001; Wright et al. 2008), and only IL-17F binds to IL-17RC in the mouse (Kuestner et al. 2007), it seems likely that IL-17A and IL-17F differentially use these receptors. In fact, the effects of IL-17A and IL-17F are different among colonic epithelial cells, macrophages, and T cells; both IL-17A and IL-17F can induce neutrophil chemo-attractants and β-defensins in colonic epithelial cells, while only IL-17A can efficiently induce cytokines in macrophages and T cells (Ishigame et al. 2009; Lin et al. 2009). These results suggest that in addition to the different binding affinity of these cytokines to these receptors, the distribution of IL-17RA and IL-17RC may determine the biological activity of IL-17A and IL-17F. It is also possible that receptors with compositions other than IL-17RA–IL-17RC heterodimer complex may determine the cell-type specificity among different cell types. Indeed, IL-17RA and IL-17RC may also form homodimers (Kramer et al. 2006). Recent findings show that IL-17RA also forms combined with IL-17RB to transduce IL-25 signaling (Rickel et al. 2008), suggesting that IL-17RA serves as a common receptor for several IL-17 family members. Further studies to elucidate the ligand–receptor relationship in the IL-17 system are needed to address these issues.

The IL-17 family members use a unique signaling pathway (Gaffen 2009). IL-17A activates the MAP kinase, NF-κB, PI3-Akt, and C/EBPδ pathways. It has also been shown that IL-17RA signaling, like IL-1/Toll-like receptor (TLR) signaling, is dependent on TRAF6. Although IL-17A shows biological activities similar to IL-1 in several immune responses, the adaptor molecules MyD88, TRIF, and IRAK4 are not required for IL-17A signaling. Recent studies showed that Act1, which physically interacts with IL-17RA and mediates TRAF6 recruitment, is an essential adaptor protein for IL-17A and IL-17F signaling and function (Li 2008; Gaffen 2009).

2 Regulation of IL-17A and IL-17F Production

Upon antigenic stimulation, naive $CD4^+$ T cells differentiate into distinct functional T cell subsets including T_H1 and T_H2 cells that are characterized by different cytokine production profiles and effector functions (Fig. 2). T_H1 cells produce large quantities of IFN-γ and mediate cellular immunity, while T_H2 cells are involved in humoral immunity and mainly produce IL-4, IL-5, and IL-13. IL-12 induces the differentiation of naive $CD4^+$ T cells into IFN-γ-producing T_H1 cells through STAT4 activation. IFN-γ signals are transduced by STAT1, which activates the downstream transcription factor, T-bet, that enhances the expression of T_H1 cell-specific genes. In contrast, IL-4 induces STAT6 activation, followed by the expression of GATA-3, a transcription factor essential for both IL-4 production and T_H2 cell differentiation. Recently, a new $CD4^+$ T cell subset (T_H17) that preferentially produces IL-17A, IL-17F, IL-9, IL-21, and IL-22 was identified. T_H17 cells have been widely accepted as important effector cells in the development of auto-immune and allergic diseases and host defenses against a group of pathogens.

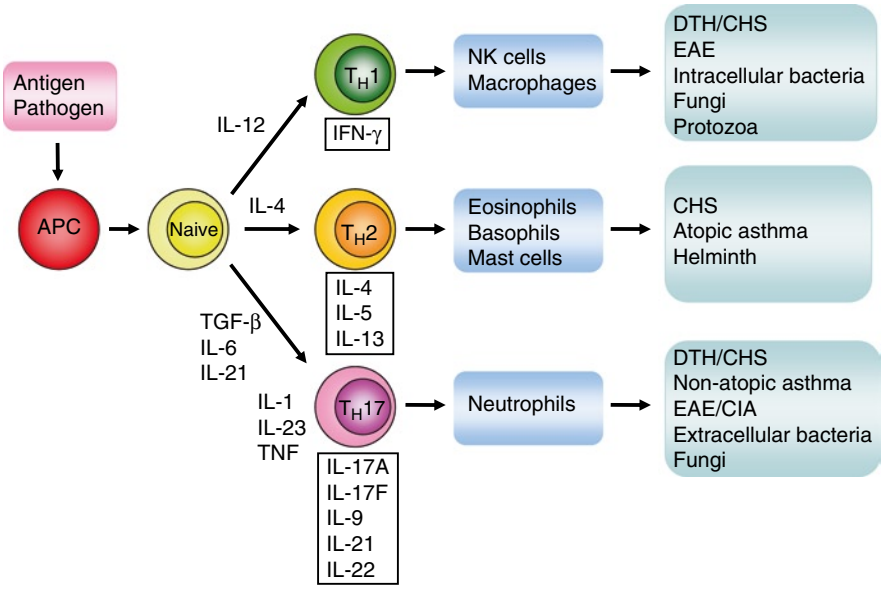

Fig. 2 Effector function of Th cell subsets

IL-17A was originally described as a product of memory $CD4^+$ T cells. The discovery of the link between IL-17A-producing T cells and IL-23 effector function led to the concept that IL-17A-producing T_H17 cells belong to a $CD4^+$ T cell subset that is distinct from the classical T_H1 and T_H2 cell subsets (Dong 2008; McGeachy and Cua 2008). Subsequent studies showed that T_H17 cell differentiation is induced by TGF-β plus IL-6 or IL-21 and accelerated by the coordinated activities of IL-1 and TNF (Fig. 2). Furthermore, T_H17 cell differentiation depends on transcription factors, including interferon-regulatory factor 4 (IRF4), aryl hydrocarbon receptor (AHR), STAT3, retinoic acid receptor-related orphan receptor α (RORα), and RORγ. It is now accepted that IL-23 is required for the growth, survival, and effector functions of T_H17 cells and promotes IL-17A, IL-17F, IL-9, IL-21, and IL-22 production by this T cell subset.

It is reported that T_H17 lineage is a heterogenous population. In addition to IL-17A and IL-17F double-positive cells, there is an IL-17A- or IL-17F single-positive population. Regulation of IL-17A and IL-17F production is also different, as IL-17F is expressed early in T_H17 development compared to IL-17A (Liang et al. 2007; Lee et al. 2009), suggesting that IL-17A and IL-17F production are regulated differently, depending on the stage of distinction. Although underlying molecular mechanisms are still not identified, it is likely that some factors, such as transcriptional factors or T cell receptor (TCR) signal strength, may distinctly regulate these productions. Indeed, deficiency of RORα only selectively reduces IL-17A, but not

IL-17F production (Yang et al. 2008b), and expression of IL-17A is more sensitive to the strength of TCR signaling compared to that of IL-17F (Gomez-Rodriguez et al. 2009). Furthermore, there are other sub-populations of T_H17 cells that selectively produce IL-9, IL-21, or IL-22, and the development of these subsets is differentially regulated (Annunziato and Romagnani 2009).

In addition to T_H17 cells, a wide variety of immune cells, including $CD8^+$ T cells, γδ T cells, and NKT cells, produce IL-17A and IL-17F under various conditions. It is likely that IL-17A production from $CD8^+$ T cells is dependent on TGF-β/IL-6 and IL-23 (He et al. 2006; Stumhofer et al. 2006). IL-23, but not IL-6, is required for IL-17A production from NKT and γδ T cells (Shibata et al. 2007; Rachitskaya et al. 2008). These cells constitutively express IL-23R and RORγt, unlike naive $CD4^+$ T cells (Lochner et al. 2008; Rachitskaya et al. 2008). Innate immune cells, such as neutrophils (Ferretti et al. 2003; Hoshino et al. 2008), monocytes (Starnes et al. 2001; Hue et al. 2006), NK cells (Satoh-Takayama et al. 2008), and lymphoid tissue inducer-like cells (LTi-like cells) (Luci et al. 2009; Sanos et al. 2009; Takatori et al. 2009), also produce IL-17A. It has now become evident that IL-17A production by these cells also contributes to various immune responses.

3 The Role of IL-17A and IL-17F in Allergic Responses

3.1 Delayed-Type Hypersensitivity

Delayed-type hypersensitivity (DTH) responses are elicited by immunization with exogenous antigens such as cells, protein antigens, and pathogens, and are believed to be mediated by $CD4^+$ T cells, especially T_H1 cells (Fig. 2). The contribution of IFN-γ in the induction of DTH is different among antigens. *Ifng*$^{-/-}$ mice have suppressed KLH-mediated DTH (Akahira-Azuma et al. 2004; Gao et al. 2006), but exacerbated OVA- and mBSA-induced DTH (Feuerer et al. 2006; Irmler et al. 2007). Thus, the pathogenic mechanism of DTH cannot be explained completely by the action of IFN-γ. Recent studies using *Il17a*$^{-/-}$and *Il17f*$^{-/-}$ showed that *Il17a*$^{-/-}$, but not *Il17f*$^{-/-}$ mice had attenuated mBSA-induced DTH (Ishigame et al. 2009). mBSA-specific T cell proliferation and mBSA-specific Ab production were also impaired in *Il17a*$^{-/-}$ mice, whereas *Il17f*$^{-/-}$ mice did not have this defect (Nakae et al. 2002; Ishigame et al. 2009). *Il17a*$^{-/-}$, but not *Il17f*$^{-/-}$, mice also showed significantly decreased KLH-specific Ab production (Yang et al. 2008a). In addition, similar to *Il17a*$^{-/-}$ mice, *Il23a*$^{-/-}$ mice show attenuated DTH responses against mBSA (Ghilardi et al. 2004). In these mice, antigen-specific T cell expansion and cytokine production (IL-2, IFN-γ, IL-4, IL-10, and GM-CSF) were normal, while IL-17A production was markedly impaired (Ghilardi et al. 2004). These observations suggest that IL-17A, rather than IL-17F, is important in DTH response. The relative contribution of IL-17A and IFN-γ in DTH response induced by different types of antigen has not yet been examined.

3.2 Contact Hypersensitivity

Contact hypersensitivity (CHS), which is induced by an epicutaneous exposure to chemicals, is considered to be a classic DTH response. Recently however, CHS is thought to be a different type of hypersensitive response, because the roles of $CD4^+$ T cells and $CD8^+$ T cells are opposite in these systems. $CD4^+$ T cells play effector function and $CD8^+$ T cells play regulatory role in DTH, while their functions are opposite in CHS (Grabbe and Schwarz 1998; Kimber and Dearman 2002). Involvement of T_H1- and IFN-γ-producing $CD8^+$ T cells (Tc1 cells) is suggested in CHS because a defect in IFN-γ signaling suppresses FITC-induced CHS response (Lu et al. 1998). Other reports demonstrate that IFN-γ is not pathogenic in oxazolone, TNCB, or DNFB-induced CHS (Saulnier et al. 1995; Lu et al. 1998; Reeve et al. 1999; Nakae et al. 2003a), suggesting involvement of other T cell subsets. In CHS induced by TNCB and DNFB, but not by oxazolone, the response is attenuated in *Il4*$^{-/-}$ mice, suggesting that T_H2 cells mediate the response (Berg et al. 1995; Weigmann et al. 1997; Dieli et al. 1999; Traidl et al. 1999). Consistently, CHS responses induced by TNCB, DNFB, FITC, and oxazolone are remarkably reduced in *Stat6*$^{-/-}$ mice (Yokozeki et al. 2000; Takeshita et al. 2004). IL-13, however, is not essential for the induction of CHS by DNFB (Herrick et al. 2003). These observations suggest that both IFN-γ and IL-4 differentially regulate CHS responses, depending on the mouse genetic background and chemicals used.

IL-17A has also been suggested in the pathogenesis of contact dermatitis because nickel-specific T cell clones established from contact dermatitis patients produce IL-17A (Albanesi et al. 1999). Both IL-17A and IL-17F strongly induce IL-6, IL-8, CXCL1, GM-CSF, SCF, and ICAM-1 expression/production in human keratinocytes (Fig. 1). CHS responses induced by TNCB, DNFB, or FITC are attenuated in *Il17a*$^{-/-}$ mice, while *Il17f*$^{-/-}$ mice display similar CHS response (Nakae et al. 2002; Oboki et al. 2008; Ishigame et al. 2009). Although IL-17A enhances T cell activation by promoting DC maturation (Antonysamy et al. 1999), an IL-17A deficiency does not affect dermal DC/Langerhans cell functions such as migration, maturation, and antigen presentation in the CHS response (Nakae et al. 2002). Instead, IL-17A is important for hapten-specific $CD4^+$, but not $CD8^+$, T cell expansion in the sensitization phase (Nakae et al. 2002). Wild-type mice engrafted with DNFB-sensitized *Il17a*$^{-/-}$ $CD4^+$ cells also exhibited reduced sensitivity to CHS (Nakae et al. 2002). It was suggested that IL-17A-producing $CD8^+$ T cells (Tc17 cells) are also important for the induction of CHS, because CHS induced by adaptive transfer of DNFB-sensitized $CD8^+$ T cell are suppressed in *Il17ra*$^{-/-}$ mice (He et al. 2006, 2009). These results indicate that IL-17A, but not IL17F, is responsible for the development of CHS in an IL-17RA-dependent manner, and IL-17A is involved in both sensitization and elicitation phases of CHS. However, relative contribution of T_H17 and Tc17 cells, and the molecular mechanisms by which IL-17A, IFN-γ and IL-4 orchestrate the development of CHS remain to be elucidated.

3.3 Allergic Airway Inflammation

Allergic asthma is mostly classified into two types: T_H2-type (atopic) and non-T_H2-type (non-atopic) (Oboki et al. 2008). Atopic asthma is characterized by an increase in serum IgE and the accumulation and activation of T_H2 cells, eosinophils, and mast cells, while non-atopic asthma is characterized by the accumulation of IL-8$^+$ cells, neutrophils, and mast cells, without elevated serum IgE (Amin et al. 2000). IL-17A and IL-17F mRNA and protein were increased in asthmatic patients compared to healthy subjects. Protein levels were profoundly elevated in the sputum of severe asthmatic patients with increased neutrophilia. IL-17A and IL-17F can activate bronchial fibroblasts, epithelial cells, and smooth muscle cells to produce various pro-inflammatory mediators such as IL-6, IL-8 and CXCL1, which are important for granulopoiesis and neutrophil recruitment (Fig. 1) (Oboki et al. 2008). IL-17A or IL-17F overexpression resulted in the induction of neutrophilia rather than eosinophilia in the lungs of rodents (Oda et al. 2005; Park et al. 2005; Yang et al. 2008a). Collectively, these observations suggest that both IL-17A and IL-17F contribute to the pathogenesis of non-atopic asthma rather than atopic asthma.

T_H2-dominant airway eosinophilia induced by immunization with OVA and antigens from fungi, cockroaches, or house dust mites is a well established rodent model for atopic asthma. Airway hypersensitivity responses (AHR) and inflammation in the lung induced by OVA with aluminum hydroxide (alum) immunization are normally induced in *Il17a*$^{-/-}$ mice and is associated with increased IL-4 and IL-5 levels in the bronchoalveolar lavages (BALs) (Nakae et al. 2002; Pichavant et al. 2008; Ishigame et al. 2009). By contrast, other studies reported that *Il17ra*$^{-/-}$ mice and *Il17a*$^{-/-}$ mice exhibit reduced pulmonary eosinophilia (Schnyder-Candrian et al. 2006; Yang et al. 2008a). IL-17F is not involved in this response because *Il17f*$^{-/-}$ mice have exacerbated or normal pulmonary eosinophilia during OVA/alum-induced airway inflammation (Yang et al. 2008a; Ishigame et al. 2009). These apparent discrepancies may be explained by different experimental conditions, such as sensitization protocols, immunization routes, antigens, and mouse backgrounds. In this regard, the molecular mechanism for the induction of airway inflammation and AHR induced by OVA changes depending on the adjuvant, such as alum (Oboki et al. 2008). He et al. showed that epicutaneous OVA sensitization potently induces T_H17 cells in the draining LNs, spleen, and lungs and recruits neutrophils in BALs, while intraperitoneal OVA immunization with alum induces weak T_H17 cell development and neutrophil recruitment (He et al. 2007). The eosinophil influx in the lungs was not affected by anti-IL-17A mAb treatment in mice epicutaneously immunized with OVA, whereas neutrophil recruitment was inhibited under these conditions. Intraperitoneal OVA sensitization with alum induced T_H17 cells in the spleen but not in the draining LNs (He et al. 2007). On the other hand, subcutaneous OVA immunization with alum did not induce T_H17 cells in the spleen, but did induce T_H17 cells in the draining LNs (Schnyder-Candrian et al. 2006). In this case, the eosinophil influx in the lungs was exacerbated by anti-IL-17A mAb treatment. Thus, T_H17 cell development in the spleen after OVA sensitization is influenced by the

immunization route (epicutaneously >> intraperitoneally > subcutaneously), and this may explain the differences in IL-17A dependency among T_H2 cell-mediated and eosinophil-dominant murine asthma models.

In contrast to T_H2 cell-dominant eosinophilic asthma models, the importance of IL-17A in the pathogenesis of non-T_H2-type neutrophilic asthma models has been clearly shown in mice (Fig. 2). OVA-specific TCR-expressing DO11.10 and OTII mice exhibit AHR and airway inflammation after OVA inhalation without prior OVA sensitization (Knott et al. 2000; Wilder et al. 2001). Similar to non-atopic asthma (Amin et al. 2000), airway inflammation in OVA-inhaled DO11.10 and OTII mice is characterized by a predominant infiltration of neutrophils rather than eosinophils in the lungs without total and OVA-specific IgE elevation in sera (Knott et al. 2000; Wilder et al. 2001; Nakae et al. 2007). In addition, T_H1 cells and T_H17 cells, but not T_H2 cells, were increased in BALs from OVA-inhaled OTII mice (Nakae et al. 2007). OVA-induced airway neutrophilia in DO11.10 and OTII mice was profoundly suppressed by the deficiency of IL-17A, whereas *Il17f*$^{-/-}$ DO11.10 mice showed normal airway neutrophilia (Nakae et al. 2002, 2007; Ishigame et al. 2009). Airway inflammation was aggravated in *Ifng*$^{-/-}$ OTII mice (Nakae et al. 2007), suggesting that IL-17A, but not IL-17F, is an effector and IFN-γ is a negative regulator of this response. IL-17A induces TNF production by mast cells independent of IgE-mediated signals, leading to neutrophil influx in airways (Nakae et al. 2007). Thus, TNF functions downstream of IL-17A in the antigen-induced airway neutrophilia in the OTII model, while IL-6 is not required in this model (Tanaka et al. 2009).

Neutrophil-dominant airway inflammation also can be induced by OVA inhalation without prior OVA sensitization in mice adoptively transferred with DO11.10 T_H17 cells (Liang et al. 2007). In this setting, T_H17 cell-derived IL-17A, rather than IL-17F, is responsible for neutrophil recruitment to the airway since T_H17 cell-mediated airway neutrophilia is suppressed by an anti-IL-17A neutralizing mAb but not by an anti-IL-17F mAb (Liang et al. 2007). Likewise, *Rag2*$^{-/-}$ mice engrafted with *Tbx21*$^{-/-}$ DO11.10 CD4$^+$ T cells, which contain a larger amount of T_H2 cells and T_H17 cells (but fewer T_H1 cells) than wild-type DO11.10 CD4$^+$ T cells, show increased eosinophil and neutrophil counts in BALs compared to *Rag2*$^{-/-}$ mice engrafted with wild-type DO11.10 CD4$^+$ T cells (Fujiwara et al. 2007). Treatment with an anti-IL-17A neutralizing mAb suppressed neutrophil, but not eosinophil recruitment in *Tbx21*$^{-/-}$ DO11.10 CD4$^+$ T cell-transferred *Rag2*$^{-/-}$ mice after OVA inhalation (Fujiwara et al. 2007), indicating that IL-17A is responsible for the neutrophil accumulation.

Neutrophil-dominant allergic airway inflammation is also elicited by inhalation of fungal antigens (proteinase from *Aspergillus oryzae*) in mice independently of T and B cells (Kiss et al. 2007). In contrast to active and passive models using DO11.10 or OTII mice, fungal proteinase-induced airway neutrophilia was normal in *Il17a*$^{-/-}$ mice but was significantly attenuated in *Il17f*$^{-/-}$ or *Il17ra*$^{-/-}$ mice (Yang et al. 2008a), indicating that IL-17F, rather than IL-17A, is responsible for fungus-induced airway neutrophilia in an IL-17RA-dependent manner.

Taken together, IL-17A, and to a lesser extent IL-17F, plays more important role in the induction of non-T_H2-type neutrophilic airway inflammation than in T_H2-type eosinophilic airway inflammation.

4 The Role of IL-17A and IL-17F in Auto-immunity

4.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is one of the most serious auto-immune diseases, mainly affecting multiple joints of the body. The development of RA was previously believed to be mediated by T_H1 cells because high levels of IL-12 and IFN-γ were detected in inflammatory sites (Feldmann et al. 1996; Gately et al. 1998). It is now clear, however, that T_H17 cells play crucial roles in this disease (Fig. 2) (Tesmer et al. 2008). Inhibition of either TNF, IL-1, or IL-6 activity in RA patients shows prominent beneficial effects on disease progression (Feldmann and Maini 2008). The roles of cytokines in the development of arthritis have been extensively examined using mouse models with different cytokine dependency.

Collagen-induced arthritis (CIA) is a typical induced arthritis model that is produced by immunizing animals with type II collagen (IIC). The development of CIA is largely dependent on IL-23, as *Il23a*$^{-/-}$ mice, but not *Il12a*$^{-/-}$ mice, are resistant to disease (Murphy et al. 2003). Both IL-17A and IL-17F are expressed in RA synovium and activates synoviocytes, fibroblasts, and endothelial cells to induce various inflammatory cytokines and chemokines, including IL-1 and TNF (Fig. 1). IL-17A also directly promotes osteoclast differentiation by inducing RANKL in osteoblasts (Sato et al. 2006). The development of this arthritis critically depends on IL-17A. *Il17a*$^{-/-}$ mice displayed significantly less severe arthritis development (Table 1) (Nakae et al. 2003b; Ishigame et al. 2009). The sensitization of T cells following immunization with IIC and IIC-specific antibody production were significantly reduced in *Il17a*$^{-/-}$ mice (Nakae et al. 2003b). These results suggest that IL-17A is involved in T cell sensitization and antibody production in addition to pro-inflammatory cytokine induction in the effector phase. As the deficiency of IL-17A could not completely suppress CIA, involvement of IL-17F was suggested. Although adoptive transfer of IL-17F gene-transduced $CD4^+$ T cells exacerbated arthritis (Yamaguchi et al. 2007), CIA was developed normally in *Il17f*$^{-/-}$ mice (Ishigame et al. 2009), indicating that IL-17A plays a more important role than IL-17F in this model. On the other hand, *Il22*$^{-/-}$ mice significantly suppressed the disease (Geboes et al. 2009) and blockade of IL-21 signaling by IL-21R-Fc fusion protein also attenuated the development of CIA (Young et al. 2007). The development of arthritis was also markedly suppressed in either *Il1α*$^{-/-}$ *Il1β*$^{-/-}$ or *Il6*$^{-/-}$ mice (Alonzi et al. 1998; Saijo et al. 2002). These observations suggest that IL-17A, IL-22 and IL-21 corporately induce arthritis development downstream of IL-23, IL-1, and IL-6.

Various animal disease models other than CIA have been developed, including spontaneous, induced, and gene-manipulated animal models. The importance of IL-17A in the development of arthritis is also reported in several RA models. Transgenic mice carrying the HTLV-1 *Tax* gene with its own LTR promoter (HTLV-I Tg mice) developed chronic inflammatory polyarthropathy resembling RA in humans at a high incidence (Iwakura et al. 1991). The expression of pro-inflammatory cytokine genes, including IL-1α, IL-1β, IL-2, IL-6, TNF, IFN-γ, and IL-17A, is

Table 1 Knockout mouse phenotypes associated with T_H1/T_H17-related cytokines in auto-immune disease models

Auto-immune disease model					
Deficient mice	CIA	EAE	$CD4^+$ $CD45RB^{hi}$ T cell-induced colitis	DSS-induced colitis	Type I diabetes
IFN-γ/IFN-γR	↑ (Vermeire et al. 1997; Guedez et al. 2001)	↑ (Ferber et al. 1996; Krakowski and Owens 1996; Willenborg et al. 1996)	↓ (Ito and Fathman 1997)	→ (Suzuki et al. 2001)	→ (Hultgren et al. 1996; Kanagawa et al. 2000; Serreze et al. 2000)
IL-17A	↓ (Nakae et al. 2003b; Ishigame et al. 2009)	↓ (Komiyama et al. 2006; Yang et al. 2008a; Ishigame et al. 2009), → (Haak et al. 2009)	→ (Noguchi et al. 2007; Izcue et al. 2008; Leppkes et al. 2009), ↑ (O'Connor et al. 2009)	↑ (Yang et al. 2008a), ↓ (Ito et al. 2008)	ND
IL-17F	→ (Ishigame et al. 2009)	→ (Yang et al. 2008a; Haak et al. 2009; Ishigame et al. 2009)	→ (Leppkes et al. 2009)	↓ (Yang et al. 2008a)	ND
IL-9/IL-9R	ND	↓ (Nowak et al. 2009)	ND	ND	ND
IL-21/IL-21R	↓ (Young et al. 2007)	↓(Korn et al. 2007; Nurieva et al. 2007), ↑ (Coquet et al. 2008; Liu et al. 2008)	↓ (Fina et al. 2008)	↓ (Fina et al. 2008)	↓ (Spolski et al. 2008; Sutherland et al. 2009)
IL-22	↓ (Geboes et al. 2009)	→ (Kreymborg et al. 2007)	↑ (Zenewicz et al. 2008)	↑ (Zenewicz et al. 2008)	ND

↑: aggravated, →: no difference, ↓: suppressed, ND: not determined

EAE experimental auto-immune encephalomyelitis, *CIA* collagen-induced arthritis, *DSS* dextran sodium sulfate

Table 2 Cytokine dependency of spontaneous RA models

	IL-1	IL-6	TNF	IL-17A	IL-17F
HTLV-I Tg	↓ (Saijo et al. 2002)	↓ (Iwakura et al. 2008)	→ (Iwakura et al. 2008)	↓ (Iwakura et al. 2008)	ND
Il1rn$^{-/-}$	ND	→ (Iwakura et al. 2008)	↓↓ (Horai et al. 2004)	↓↓ (Nakae et al. 2003c)	↓ (Ishigame et al. 2009)
SKG	↓ (Hata et al. 2004)	↓↓ (Hata et al. 2004)	↓ (Hata et al. 2004)	↓↓ (Hirota et al. 2007a, b)	ND

→: independent, ↓: involved, ↓↓: dependent, ND: not determined
HTLV-I human T cell leukemia virus type I, *Il1rn* IL-1R antagonist

enhanced in transgenic joints (Iwakura et al. 1995). The development of arthritis was greatly suppressed in either *Il1α*$^{-/-}$*Il1β*$^{-/-}$, *Il6*$^{-/-}$, or *Il17a*$^{-/-}$ HTLV-I Tg mice (Table 2) (Iwakura et al. 2008), indicating the importance of these cytokines in the development of arthritis in this model. Excess IL-6 signaling enhances the development of arthritis, as the development of arthritis is accelerated in HTLV-I Tg mice carrying a Y759F mutation in the IL-6R gp130 which is important for SOCS3-mediated negative feedback (Ishihara et al. 2004). In contrast, a TNF deficiency did not affect disease development at all (Iwakura et al. 2008). An IFN-γ and IL-4 deficiency also did not affect disease onset (Iwakura et al. 2008), suggesting that neither T_H1 nor T_H2 cells are involved in the pathogenesis of this arthritis.

Similar cytokine dependency is also observed in SKG mice, which develop autoimmune arthritis because of a mutation in ZAP 70 of the TCR complex. An IL-17A deficiency completely suppresses the development of arthritis (Table 2) (Hirota et al. 2007a, b). Consistent with this result, the development of arthritis in SKG mice depends on IL-6, IL-1, and TNF (Hata et al. 2004; Hirota et al. 2007a, b), indicating that these cytokines play important roles in the pathogenesis. The role of IL-17F, IL-21 and IL-22 in these models remains to be elucidated.

K/BxN mice carry the KRN transgene, which encodes a TCR reactive against a peptide from glucose-6-phosphate isomerase (GPI) presented by the A^{g7} MHC class II molecule (Matsumoto et al. 1999). KRN-transgenic mice on the NOD (A^{g7}) background spontaneously develop auto-immune arthritis. The development of arthritis in this model depends on both T cells and B cells, and serum from K/BxN mice can induce arthritis in recipient mice (Korganow et al. 1999). Auto-antibodies to GPI are responsible for the disease (Matsumoto et al. 1999) because immune complexes activate the C5a-containing complement activation pathway in mast cells through FcγRIII, resulting in the induction of inflammatory cytokines (Ji et al. 2002a; Nigrovic et al. 2007). It was shown that mast cell-derived IL-1 plays a crucial role in the development of arthritis in this serum transfer model (Nigrovic et al. 2007). In addition, TNF is involved in the development of arthritis in this model (Ji et al. 2002b). Neutralization of IL-17A does not affect K/BxN serum induced arthritis, indicating that IL-17A is not required in the effector phase. In this model however, autoreactive KRN T cells enhance K/BxN serum-transferred arthritis in a

IL-17 dependent manner, suggesting that IL-17 can enhance inflammation to some extent even in this setting (Jacobs et al. 2009).

It is widely accepted that IL-1 is a potent inducer of IL-17A and IL-17F production (Fig. 2). IL-1 receptor antagonist (Ra) is an endogenous negative regulator of IL-1 signaling and IL-1Ra deficient (*Il1rn*$^{-/-}$) mice spontaneously develop chronic inflammatory arthropathy (Horai et al. 2000). The IL-17A and IL-17F-producing T cell population is significantly expanded in the LNs of *Il1rn*$^{-/-}$ mice (Nakae et al. 2003c; Ishigame et al. 2009), suggesting that IL-1Ra deficiency may be sufficient to render T cells highly sensitive to IL-1, thereby leading to the activation of autoreactive IL-17A and IL-17F producing T cells by a physiological level of IL-1 in vivo. Interestingly, the development of arthritis in *Il1rn*$^{-/-}$ mice was almost completely suppressed in *Il17a*$^{-/-}$ *Il1rn*$^{-/-}$ mice (Nakae et al. 2003c), and slightly suppressed in *Il17f*$^{-/-}$ *Il1rn*$^{-/-}$ mice (Table 2) (Ishigame et al. 2009). In contrast, the deficiency of T-bet does not affect the development of arthritis (Wang et al. 2006), suggesting that T_H17 cells, not T_H1 cells, are involved in the pathogenesis of this model. A TNF deficiency also completely suppressed the development of arthritis in these mice (Horai et al. 2004). In contrast to HTLV-I Tg and SKG mice, *Il6*$^{-/-}$ *Il1rn*$^{-/-}$ mice did not suppress disease onset (Iwakura et al. 2008), signifying that IL-1 can bypass the requirement of IL-6 for T_H17 cell differentiation. Several studies have been reported that IL-1 directly acts on $CD4^+$ T cells to produce IL-17A (Ben-Sasson et al. 2009; Chung et al. 2009), although underlying mechanisms are unknown. Several reports have shown that IL-6 is not absolutely required for T_H17 differentiation. IL-21 can substitute for IL-6 to induce T_H17 cell development in an autocrine manner (Korn et al. 2007; Nurieva et al. 2007; Zhou et al. 2007). Furthermore, IL-6 is not required for the induction of IL-17A from NKT cells or γδ T cells (Shibata et al. 2007; Rachitskaya et al. 2008). Further study is necessary to address whether IL-1 alone can directly induce IL-17A production/T_H17 differentiation under certain conditions in vivo, or which T cell subset is the direct target for IL-1 to induce auto-immune arthritis in this model.

The role of TNF in RA is well established, as anti-TNF Ab treatment has been proved to be efficient for most RA patients (Feldmann and Maini 2008). However, a minor proportion of the patients are refractory against this treatment. It is possible that other cytokines such as IL-1, IL-6, and IL-17A are activated in these patients like HTLV-I Tg mouse model, which develop TNF-independent auto-immune arthritis. Because these cytokines act independently in the development of arthritis as revealed by these disease models, inhibitors for IL-17A, TNF, and IL-6 may be used in a complementary manner in the treatment of RA.

4.2 Experimental Auto-immune Encephalomyelitis

Experimental auto-immune encephalomyelitis (EAE) is a well established murine model of multiple sclerosis (MS) and has long been believed to be a T_H1 cytokine-mediated auto-immune disease (Kuchroo et al. 2002). However, the mechanisms of

EAE development are more complex than previously thought. EAE is much more severe in mice which are defective in IL-12/IFN-γ activity (Gran et al. 2002; Zhang et al. 2003), arguing against the importance of T_H1 cells in this disease. Several studies have demonstrated that IL-23, rather than IL-12 is essential for EAE development, as EAE was greatly attenuated in mice that lack an IL-23 signal (Cua et al. 2003; Zhang et al. 2003). Consistent with these observations, *Il17a*$^{-/-}$ mice were resistant to EAE (Table 1) (Komiyama et al. 2006; Yang et al. 2008a; Ishigame et al. 2009). However, one report claimed that IL-17A did not contribute to EAE development because CD4$^+$ T cell-specific IL-17A overexpression did not have a major impact on the development of EAE (Haak et al. 2009). It was not shown whether the IL-17A expression levels in these transgenic mice were enough for the development of EAE. In support of the importance of T_H17 cells, the development of EAE was also diminished in *Rorγ*$^{-/-}$ and *Rorα*$^{-/-}$ mice which lacked T_H17 cells (Ivanov et al. 2006; Yang et al. 2008b). Unlike the *Il23a*$^{-/-}$ mice, *Il17a*$^{-/-}$ mice still developed significant inflammation after MOG immunization, proposing that other IL-23-induced mediators, such as IL-17F and IL-22 may also contribute to the development of EAE. IL-17F, however, is not required for the pathogenesis of EAE (Yang et al. 2008a; Haak et al. 2009; Ishigame et al. 2009). Mice deficient in both IL-17A and IL-17F showed no additional suppression (Ishigame et al. 2009), showing that IL-17F is not only dispensable for the induction of these responses, but also does not have any substantial additive, synergistic, or compensatory effects to those of IL-17A in these disorders. T_H17 cell-derived IL-17A, as well as IL-22, disrupts tight junctions that form the blood-brain barrier, resulting in an infiltration of T_H17 cells into the central nervous system (Kebir et al. 2007) It is shown that IL-22 is also dispensable for EAE development (Kreymborg et al. 2007), while the contribution of IL-21 in the induction of EAE is still controversial. Although recombinant IL-21 can induce T_H17 cell differentiation from naive T cells in the presence of rhTGF-β in vitro, endogenous IL-21 is not essential for the T_H17 cell differentiation during EAE in vivo. EAE development is suppressed in some reports using *Il21*$^{-/-}$ and BALB/c-*Il21r*$^{-/-}$ mice (Korn et al. 2007; Nurieva et al. 2007), but is aggravated in other reports using the C57BL/6-*Il21*$^{-/-}$ and -*Il21r*$^{-/-}$ mice (Coquet et al. 2008; Liu et al. 2008). Recent studies also demonstrated that IL-9 produced by T_H17 cells is also involved in EAE development (Nowak et al. 2009). However, IL-9 blockade by antibody or IL-9R deficiency only partially ameliorates disease. Therefore, the downstream mechanism of IL-23 still remains to be elucidated.

In contrast to the results observed from mice lacking IL-12 or IL-23 signaling, EAE can be induced by transfer of either IL-12 or IL-23-stimulated CD4$^+$ T cells (Kroenke et al. 2008; Lees et al. 2008; Stromnes et al. 2008). Patterns of CNS infiltration and cytokine requirement in disease development are quite different between each T_H cell-transplanted mice. The majority of CNS infiltrating cells from recipient mice of IL-12-stimulated CD4$^+$ T cells are macrophages and lymphocytes, whereas significant neutrophil recruitment is observed in mice given IL-23-stimulated CD4$^+$ T cells (Kroenke et al. 2008; Lees et al. 2008; Stromnes et al. 2008). Neutralization of either IL-17A or GM-CSF delayed onset of disease induced by IL-23-stimulated CD4$^+$ T cells, whereas IL-12-stimulated CD4$^+$ T cell-mediated disease was not

(Kroenke et al. 2008). Induction of EAE mediated by ether cell types was not dependent on IFN-γ, because neither IL-12 or IL-23-mediated disease was suppressed by the treatment of anti-IFN-γ antibody (Kroenke et al. 2008). Several reports suggest that the T_H17/T_H1 ratio of infiltrating cells determines the sites of inflammation within the CNS (Kroenke et al. 2008; Lees et al. 2008; Stromnes et al. 2008). These observations suggest that T_H17 and T_H1 cell contribute to induction of EAE by using different pro-inflammatory pathways, and the balance between T_H1 and T_H17 cells is critical for the pathogenesis of EAE.

It is believed that T_H17 cell-derived IL-17A is required for the induction of EAE because $CD4^+$ T cells from *Il17a*$^{-/-}$ mice could not efficiently induce EAE (Komiyama et al. 2006). Several studies showed that IL-17A-producing γδ T cells are also important for the development of EAE. γδ T cell-deficient mice showed a delayed onset and reduced severity of EAE (Jensen et al. 2008). γδ T cells isolated from MOG-immunized mice could rapidly induce IL-17A production compared to that of T_H17 cells after in vitro re-stimulation, and this IL-17A induction is mediated by IL-1 and IL-23 (Sutton et al. 2009). These γδ T cells were able to promote IL-17A production by $CD4^+$ T cells as well as disease susceptibility, suggesting that IL-17A producing γδ T cells cooperate with $CD4^+$ T cells to induce EAE. IL-17A producing γδ T cells are also increased in the arthritic joints and deletion of $V\gamma4^+$ TCR, which is predominant source of IL-17A among γδ T cells during CIA and significantly reduces disease incidence (Roark et al. 2007).

4.3 Inflammatory Bowel Disease

Dysregulation of intestinal homeostasis causes inflammatory bowel diseases in which T cells play important roles. Recently, several studies have established that IL-23 is an essential cytokine for T cell-dependent intestinal inflammation. Transfer of $CD4^+CD45RB^{hi}$ T cells into lymphopenic mice is a well established model of IBD. In this model, adoptive transfer of $CD4^+CD45RB^{hi}$ T cells into IL-23 deficient *Rag*$^{-/-}$ mice could not induce colitis while wasting disease was observed in IL-12 deficient *Rag*$^{-/-}$ recipient mice (Uhlig et al. 2006). Similarly, deficiency of IL-23 suppressed the development of T cell-dependent spontaneous IBD in *Il10*$^{-/-}$ mice (Yen et al. 2006). These results indicate that IL-23, rather than IL-12, plays an important role in the intestinal inflammatory response. Consistent with these observations, naïve $CD4^+$ T cells isolated from *Rorgt*$^{-/-}$ mice induced less severe colitis (Leppkes et al. 2009), and adoptive transfer of $IL\text{-}17F^+$ $CD4^+$ T cells induced significantly rapid colitis (Lee et al. 2009). However, the role of IL-17A and IL-17F in colitis is still controversial. Neither IL-17A or IL-17F deficiency suppressed colitis in $CD4^+CD45RB^{hi}$ T cell adoptive transfer model (Table 1) (Noguchi et al. 2007; Izcue et al. 2008; Leppkes et al. 2009). Transfer of *Il17f*$^{-/-}$ $CD4^+CD45RB^{hi}$ T cells, in combination with anti-IL-17A Ab, significantly reduced colitis (Leppkes et al. 2009), suggesting that IL-17A and IL-17F have redundant function during colitis development in this model. Recent studies reported that mice transferred with

Il17a$^{-/-}$ CD4^{+} T cells displayed an accelerated wasting disease, which is associated with increased T_H1-related cytokine production, and suggests a protective function of IL-17A (O'Connor et al. 2009). It should be noted that the protective function of IL-17A is only observed in recipient mouse weight loss and the extent of cellular infiltration does not correlate with the wasting aspect of the disease. Thus, the function of IL-17A in inflammation and in maintaining homeostasis of the gut may be different. On the other hand, many studies suggest that T_H1 cells are also a key mediator in the development of IBD. Colitis was suppressed by the adoptive transfer of CD4^{+}CD45RB^{hi} T cells deficient in a T_H1 cell-associated gene, such as IFN-γ, T-bet, or STAT4. In addition, both T_H1 and T_H17 cells were required for the development of *Hericobactor hepaticus*-induced colitis downstream of IL-23 (Hue et al. 2006; Kullberg et al. 2006). It is interesting to investigate what kind of conditions determine the relative contribution of T_H1 and T_H17 cells and how other T_H17 cell-related cytokines, such as IL-17A, IL-17F, IL-22, and IL-21, are involved in the pathogenesis of T cell-mediated IBD.

The role of IL-17A in a dextran sodium sulfate (DSS)-induced acute colitis model is also still controversial. Although one study reported that *Il17a*$^{-/-}$ mice displayed significantly reduced clinical score (Ito et al. 2008), other studies demonstrated that mice deficient in IL-17A or given anti-IL-17A Ab showed severe weight loss and colonic epithelial damage (Table 1) (Ogawa et al. 2004; Yang et al. 2008a). On the other hand, *Il17f*$^{-/-}$ mice developed less severe colonic inflammation, which is associated with reduced chemokine expression (Yang et al. 2008a). IL-21 deficiency also suppressed body weight loss by inhibiting induction of T_H17 associated molecules such as IL-6, IL17A, and IL-17F (Fina et al. 2008). IL-22 has a protective role in both DSS- and CD4^{+}CD45RB^{hi} T cell-induced colitis (Zenewicz et al. 2008). This protective function of IL-22 in these models appears to be mediated not only by CD4^{+} T cell-derived IL-22, but also by NK cell-derived IL-22. Although T cell-produced IL-22 is dispensable for the protection of CD4^{+} T cell-induced colitis, deficiency of both donor and recipient derived IL-22 production resulted in more severe colitis. It has been also demonstrated that IL-23 is also a key player in T cell-independent colitis induced by an agonistic anti-CD40 antibody (Uhlig et al. 2006). Because lymphopenic mice can also produce IL-17A, IL-17F, and IL-21 from innate immune cells such as LTi-like cells, NK cells, and monocytes, further studies are needed to investigate whether these cytokines are also involved in innate immune cell-mediated IBD models.

4.4 Type I Diabetes

Type I diabetes mellitus (T1D) is an auto-immune disease caused by the invasion of islets of Langerhans by mononuclear cells resulting in the destruction of β cells. Both CD4^{+} and CD8^{+} T cells are involved in the islet destruction. Deficiency of IFN-γ or IFN-γR on the NOD background did not suppress the development of diabetes (Hultgren et al. 1996; Kanagawa et al. 2000; Serreze et al. 2000) (Table 1), suggesting that other mediators contribute to the pathogenesis. Several groups reported that

IL-17A is involved in the pathogenesis of diabetes. Both IL-17A and IL-17F expression are increased in diabetic NOD pancreas (Martin-Orozco et al. 2009). Neutralization of IL-17A by anti-IL-17A Ab treatment or suppression of IL-17A production by inducing IFN-γ restored normoglycemia at the pre-diabetic stage of NOD mice is important (Jain et al. 2008; Emamaullee et al. 2009). IL-21 also plays a key role in the development of type 1 diabetes. *Il21r*$^{-/-}$ NOD mice are highly resistant to insulitis, auto-antibody production against insulin, and diabetes development (Spolski et al. 2008; Sutherland et al. 2009). Mice expressing IL-21 in pancreatic β cells produced elevated levels of pro-inflammatory cytokines including IL-17A, IL-17F, and IFN-γ, and spontaneously developed diabetes even on the diabetes-resistant background (Sutherland et al. 2009). It is still controversial whether or not IL-21-induced diabetes depends on T_H17 cells. Further studies are required to examine the role of IL-17A and IL-17F in the pathogenesis of diabetes by using IL-17A or IL-17F deficient NOD mice.

Transfer of the diabetogenic CD4$^+$ BDC2.5 TCR$^+$ T cell into NOD.scid mice can also cause diabetes (Katz et al. 1995). In this model, it is clear that T_H1 cells play an important role in the induction of diabetes, because in vitro differentiated IFN-γ-producing BDC2.5 TCR$^+$ T_H1 cells potently induce disease (Katz et al. 1995). Recent studies showed that diabetogenic T_H17 cells can also rapidly induce diabetes in NOD.scid mice (Bending et al. 2009; Martin-Orozco et al. 2009). Interestingly, several reports showed that adoptive transfer of in vitro generated T_H17 cells and maintained their differentiation program in normal recipients, whereas these cells were reprogrammed into T_H1 cells in lymphopenic recipients (Bending et al. 2009; Lee et al. 2009; Martin-Orozco et al. 2009). Accordingly, diabetes development induced by the transfer of in vitro differentiated T_H17 cells in NOD.scid mice was dependent on IFN-γ, but not IL-17A (Bending et al. 2009; Martin-Orozco et al. 2009). In CD8$^+$ T cell-induced diabetes model, adoptive transfer of IL-23-treated OTI Tc17 cells can induce diabetes in normal recipients that express OVA under the control of rat insulin promoter, and disease development is dependent on both IL-17A and IL-17F (Ciric et al. 2009). Thus, it is interesting to study what kinds of mediators regulate the plasticity of T_H17 and Tc17 developmental program, and the impact of these on the development of auto-immunity, such as type I diabetes.

5 The Role of IL-17A and IL-17F in Host Defense Against Infections

5.1 Microbe Stimulation and IL-17A and IL-17F Production

Recent studies suggest that IL-17A and IL-17F are also involved in host defense against infection. When stimulated by microbial products through pattern recognition receptors, APCs acquire the capacity to activate naive T cells to differentiate

into effector T cells that mediate adaptive immune responses. APCs stimulated with pathogens such as *Bordetella pertusis*, *Klebsiella pneumoniae*, and *Mycobacterium tuberculosis* produce large amounts of IL-23, resulting in the development of T_H17 cells (Khader et al. 2009). Several Toll-like receptor (TLR) agonists including LPS (TLR4 ligand), CpG-containing oligonucleotides (TLR9 ligand), R848 (TLR7/8 ligand), and peptidoglycans (PGN) (TLR2 ligand) are thought to induce IL-12 production in DCs (Napolitani et al. 2005; Gerosa et al. 2008). These TLR agonists also induce IL-23 production that facilitates T_H17 differentiation (Napolitani et al. 2005; Gerosa et al. 2008) as CpG and PGN can substitute for complete Freund's adjuvant containing killed mycobacteria to induce EAE, in which T_H17 cells play a crucial role (Segal et al. 2000; Visser et al. 2005). Interestingly, in addition to TLRs, the intracellular receptor, NOD2, also plays a critical role in the generation of T_H17 cells (van Beelen et al. 2007). NOD2 recognizes muramyldipeptides (MDP), the minimal motif in PGN from bacterial cell walls. Although stimulation of DCs with MDP alone does not induce cytokine production, MDP in combination with other bacterial-derived TLR agonists enhances TLR-mediated IL-1 and IL-23 production and promotes T_H17 cell differentiation (van Beelen et al. 2007). These findings indicate that many pathogen-derived molecules can induce both IL-12 and IL-23. However, the precise conditions or mechanisms by which either IL-12 or IL-23 is preferentially induced and lead to the preferential expansion of T_H1 or T_H17 cells remain to be elucidated.

5.2 Bacterial Infection

The importance of IL-12 in host defense against various bacteria is widely accepted (Fig. 2). Mice deficient in IFN-γ, IFN-γR, or STAT1 are highly susceptible to many pathogens, including *Listeria monocytogenes*, *M. tuberculosis*, and *Salmonella enteritidis* (Shtrichman and Samuel 2001). The IL-12-IFN-γ axis is primarily involved in host defense against intracellular pathogens by activating cellular immunity to kill bacteria and infected cells. In contrast, the IL-23-IL-17A axis is thought to be critical for host defense against extracellular bacteria by inducing CXC chemokine and G-CSF production and antimicrobial peptides, such as β-defensins, lipocalin-2, and S100A family proteins in epithelial cells and keratinocytes (Fig. 1). Indeed, *Il17ra*$^{-/-}$, *IL17a*$^{-/-}$, and *Il23a*$^{-/-}$ mice are more susceptible to the extracellular bacterium *K. pneumoniae* in the lungs (Ye et al. 2001; Happel et al. 2005; Aujla et al. 2008) (Fig. 2). These mice show impaired neutrophil recruitment at the site of infection which is associated with defective G-CSF and CXC chemokine production. IL-12 and IFN-γ signaling have also been shown to be critical for host defense against *K. pneumoniae*. IL-22 is induced with kinetics that are similar to those of IL-17A and IL-17F from T_H17 cells and may also be involved in host defense mechanism. The protective role of IL-23 in colonic mucosal infection is also reported. IL-23, rather than IL-12, is required for host defense in the colon during the early phase of *Citrobacter rodentium* infection

(Mangan et al. 2006; Zheng et al. 2008). IL-17A and IL-17F are also involved in responses against *C. rodentium* by inducing β-defensin production. Notably, splenomegaly and colon hypertrophy, which are associated with severe colonic inflammation, were more pronounced in *Il17f*$^{-/-}$ mice than in *Il17a*$^{-/-}$ mice (Ishigame et al. 2009), suggesting that IL-17F is more important than IL-17A in protecting colonic epithelial cells from the pathogenic effects of this bacterium. However, a recent study using *Il22*$^{-/-}$ and *Il17rc*$^{-/-}$ mice, which do not respond to IL-17A and IL-17F, demonstrated that IL-22, but not IL-17A and IL-17F, expressed in response to IL-23 is essential for the early host response against *C. rodentium* (Zheng et al. 2008). IL-22 is produced by innate immune cells, including dendritic cells and NK cells during *C. rodentium* infection and induces the expression of Reg family antimicrobial proteins in colonic epithelial cells (Zheng et al. 2008). It is interesting to note that T_H17 cells differentiation in the gastrointestinal tract is largely dependent on commensal microbiota (Gaboriau-Routhiau et al. 2009; Ivanov et al. 2009). Germ-free mice have much fewer lamina propria T_H17 cells compared to specific-pathogen-free mice (Niess et al. 2008; Gaboriau-Routhiau et al. 2009; Ivanov et al. 2009), although one report showed increased T_H17 population in the colon due to decreased IL-25 production by colonic epithelial cells (Zaph et al. 2008). Thus, intestinal commensal bacteria may differentially influence gut immune cells, such as T_H17 cells, γδ T cells, and NK cells, causing various effects on the intestinal host immune responses.

These findings indicate that T_H17 cells and their related cytokines play critical roles in host defense against extracellular pathogens at epithelial and mucosal tissues such as the skin, lung, and intestine. T_H17 cells also appear to play important roles in humans. Subjects with mutations in STAT3, which is critical for T_H17 differentiation, often suffer from fungal and extracellular pathogen infections such as *Candida albicans* and *Staphylococcus aureus* in the skin and lung (Milner et al. 2008). T cells from these subjects fail to produce IL-17A, while IL-2, TNF, and IFN-γ production are normal (Milner et al. 2008). Similarly, *Il17ra*$^{-/-}$ or *Il17a*$^{-/-}$*Il17f*$^{-/-}$ mice are highly susceptible to opportunistic *S. aureus* infection (Schwarzenberger and Kolls 2002; Ishigame et al. 2009), whereas *Il17f*$^{-/-}$ and *Il17a*$^{-/-}$ mice show normal sensitivity to this pathogen (Ishigame et al. 2009). These results suggest that the increased susceptibility of these subjects to infection is at least partially due to impaired T_H17 cell differentiation and function, and that IL-17A and IL-17F complement each other in this setting.

Several lines of evidence have suggested that the IL-23-IL-17A axis is also required for host defense against intracellular pathogens in mice. Mice lacking both IL-12 and IL-23 are more susceptible to *M. tuberculosis* and *S. enteritidis* infections than mice lacking IL-12 alone (Holscher et al. 2001; Lehmann et al. 2001; Lieberman et al. 2004). Similar results are also reported in protozoa infection, such as *Toxoplasma gondii* (Kelly et al. 2005). *Il17ra*$^{-/-}$, *Il17a*$^{-/-}$, and *Il23a*$^{-/-}$ mice do not show increased susceptibility to *M. tuberculosis* infection (Khader et al. 2005; Umemura et al. 2007; Aujla et al. 2008) but IL-17RA signaling is required for the recruitment of T_H1 cells to the site of infection to induce a recall

response against *M. tuberculosis* following vaccination (Khader et al. 2007). Thus, T_H1 cells, rather than T_H17 cells play a more important role in host protection against intracellular bacteria. In contrast to these findings, it has been reported that the IL-23/IL-17A pathway is required for host resistance to the intracellular pathogen *Francisella tularensis* by inducing T_H1-type immune responses (Lin et al. 2009). Impaired IFN-γ production is also observed when *Il17a*$^{-/-}$ mice are infected with *Mycobacterium bovis* bacilli Calmette-Guerin (BCG) (Umemura et al. 2007), indicating that under certain conditions, IL-23/IL-17A pathway-dependent induction of T_H1 immune responses is essential for effective clearance of intracellular bacteria. Furthermore, IL-17A and IL-17F produced by γδ T cells are also involved in innate immune response against *L. monocytegenes* in the liver. IL-17A and IL-17F are mainly produced by γδ T cells at early stages of infection and deficiency of IL-17A, IL-17RA, or IL-23 results in increased bacterial burden (Hamada et al. 2008; Meeks et al. 2009). Increased IL-17A production from γδT cells is also observed when mice are infected with *M. tuberculosis*, *M. bovis* BCG, or *S. enteritidis* (Lockhart et al. 2006; Umemura et al. 2007; Siegemund et al. 2009). Further studies are required to elucidate the relative contribution of $CD4^+$ T cells and γδ T cells in IL-17A/IL-17F-mediated host protective immunity against different bacteria.

5.3 Fungal Infection

Both IL-17A and IL-17F are also induced by β-glucans, the components of yeast, fungus, and mushroom cell walls, through a TLR-independent pathway. Dectin-1 is a C type lectin receptor that is widely expressed on myeloid cells such as DCs and macrophages. Dectin-1 recognizes β-glucans in zymosans and fungi and plays an important role in host defense against fungi (Saijo et al. 2007; Taylor et al. 2007). Dectin-1 activates the Syc-CARD9 pathway through the ITAM in the cytoplasmic domain causing induction of IL-23, TGF-β, and IL-6, but little IL-12, which preferentially promotes T_H17 cell differentiation (LeibundGut-Landmann et al. 2007). Dectin-2 is another C type lectin receptor for fungi and also contributes to fungus-induced IL-17A production (Robinson et al. 2009). Unlike dectin-1, interaction of Dectin-2 with FcRγ is required for the activation of Syk-CARD9 complex because Dectin-2 has no signaling motif in the cytoplasmic domain (Robinson et al. 2009). It is reported that candida mannan also induce T_H17 response via mannose receptor (van de Veerdonk et al. 2009), suggesting that these receptors induce T_H17 response in cooperation during fungal infections. Fungal zymosans in incomplete Freund's adjuvant (IFA) show potent adjuvant activity in EAE induction upon immunization with MOG peptide (Veldhoen et al. 2006). Furthermore, β-glucans derived from *C. albicans* act as an adjuvant in CIA (Hida et al. 2005) and fungal infection causes the development of arthritis in SKG mice in which T_H17 cells play an important role (Yoshitomi et al. 2005).

A protective role for the IL-23/IL-17A pathway in fungal infections is suggested by the finding that mice lacking IL-12/IL-23 are more susceptible to systemic *Cryptococcus neoformans* infection than mice lacking IL-12 (Decken et al. 1998). An IL-23 deficiency results in increased susceptibility to *C. neoformans* infection, although IL-12 plays a more important role (Kleinschek et al. 2006). The involvement of IL-17R signaling is also evident in systemic *C. albicans* infection (Huang et al. 2004). *Il23a*$^{-/-}$ and *Il17ra*$^{-/-}$, but not *Il12a*$^{-/-}$ mice, are also highly susceptible to oral candidiasis due to defective neutrophil recruitment and antimicrobial peptide induction (Conti et al. 2009). As *Il22*$^{-/-}$ mice are only mildly susceptible to oral candidiasis, it is suggested that IL-17A and IL-17F, rather than IL-22, is important for the host defense in this model.

Although IL-23/IL-17A is required for host defense against some fungi (Fig. 2), dysregulated production of these cytokines induces tissue damage in infected tissues. It has been reported that the IL-23/IL-17A pathway promotes inflammation and susceptibility in gastric *C. albicans* and pulmonary *A. fumigatus* infections. Although IL-17R signaling is critical for systemic and oral *C. albicans* infection, both IL-17A and IL-23 impair the antifungal activities of neutrophils by negatively regulating IFN-γ-mediated induction of indoleamine 2, 3-dioxygenase (IDO) (Zelante et al. 2007; Romani et al. 2008), which has potent regulatory effects on inflammatory and T cell responses. Similarly, in chronic *T. gondii* infection, a deficiency in IL-27, which negatively regulates T_H17 cell differentiation, caused severe neuro-inflammation associated with an increased number of T_H17 cells (Stumhofer et al. 2006). Thus, IL-23 and IL-17A function in both a protective and detrimental manner, depending on the pathogen and infection conditions.

6 Concluding Remarks

Clinical studies showed that blockade of IL-12/IL-23 (p40), IL-1, IL-6 or TNF activity is effective in the treatment of inflammatory diseases, such as RA, MS, inflammatory bowel diseases, and psoriasis. As these cytokines are involved in the development of T_H17 cells, neutralization of T_H17 cell-related cytokine activity may be an attractive strategy for the treatment of these diseases in humans. However, these treatments may increase the risk of opportunistic infections, because both IL-17A and IL-17F are involved in mucosal host defense. As most of available data suggests that IL-17A is more important mediator than IL-17F in allergic and auto-immune diseases, specific neutralization of IL-17A is an attractive treatment of inflammatory diseases without compromising host defense activity.

Accumulating evidence suggests that at least three independent effector T cell pathways are involved in inflammatory responses: IL-12/T_H1, IL-4/T_H2, and IL-23/T_H17. Identifying the major immune pathways responsible for the development of each disease is important for treatment because suppression of one pathway may accelerate the others. Understanding these cytokine networks will lead to the development of more effective treatment of allergic and auto-immune diseases.

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