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REVIEW

Interleukin-17 family cytokines in protective immunity against infections: role of hematopoietic cell-derived and non-hematopoietic cell-derived interleukin-17s

Goro Matsuzaki and Masayuki Umemura

Molecular Microbiology Group, Tropical Biosphere Research Center and Department of Host Defense, Graduate School of Medicine, University of the Ryukyus, Senbaru 1, Nishihara, Okinawa 903-0213, Japan

ABSTRACT

Interleukin-17 family cytokines, consisting of six members, participate in immune response in infections and autoimmune and inflammatory diseases. The prototype cytokine of the family, IL-17A, was originally identified from CD4+ T cells which are now termed Th17 cells. Later, IL-17A-producing cells were expanded to include various hematopoietic cells, namely CD8+ T cells (Tc17), invariant NKT cells, γδ T cells, non-T non-B lymphocytes (termed type 3 innate lymphoid cells) and neutrophils. Some IL-17 family cytokines other than IL-17A are also expressed by CD4+ T cells: IL-17E by Th2 cells and IL-17F by Th17 cells. IL-17A and IL-17F induce expression of pro-inflammatory cytokines to induce inflammation and anti-microbial peptides to kill pathogens, whereas IL-17E induces allergic inflammation. However, the functions of other IL-17 family cytokines have been unclear. Recent studies have shown that IL-17B and IL-17C are expressed by epithelial rather than hematopoietic cells. Interestingly, expression of IL-17E and IL-17F by epithelial cells has also been reported and epithelial cell-derived IL-17 family cytokines shown to play important roles in immune responses to infections at epithelial sites. In this review, we summarize current information on hematopoietic cell-derived IL-17A and non-hematopoietic cell-derived IL-17B, IL-17C, IL-17D, IL-17E and IL-17F in infections and propose functional differences between these two categories of IL-17 family cytokines.

Key words interleukin-17, interleukin-17 receptor, infection.

There are six IL-17 family cytokines, IL-17A to IL-17F (1–3), and they are involved in various immune responses in infectious, autoimmune and inflammatory diseases (4–6). IL-17A (frequently cited as IL-17), the prototypic member of the family, was originally identified as a cytokine produced by the subset of CD4+ T cells that is now termed Th17 (4). T cell priming in the presence of transforming growth factor-β and inflammatory cytokines such as IL-6 and IL-1β is required for development of Th17 cells, whereas IL-23 supports their maintenance and IL-17A production. RORγt transcription factor is the master regulator of Th17 lineage commitment (4). IL-17A is also produced by CD8+ T cells (Tc17), invariant NKT cells, TCR γδ T cells, ILC3 (which lack expression of T cell and B cell receptor) and even by neutrophils (7–9). IL-17E and IL-17F are also produced by the CD4+ T cell subsets of Th2 and Th17, respectively (7, 10). However, cellular sources and targets of other IL-17 cytokines, including IL-17B, IL-17C and IL-17D, have been unclear. Recent studies have shown involvement of these cytokines in immune responses to infections, especially at epithelial sites (11–-14). Furthermore, production of IL-17E and IL-17F by epithelial cells has also been reported (15–17).

Correspondence
Goro Matsuzaki, Molecular Microbiology Group, Tropical Biosphere Research Center, University of the Ryukyus, Senbaru 1, Nishihara, Okinawa 903-0213, Japan. Tel: +81 98 895 8968; fax: +81 98 895 8944; email: matsuzak@comb.u-ryukyu.ac.jp

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List of Abbreviations: AMP, anti-microbial peptide; ILC, innate lymphoid cell; nTh17, natural Th17; TCR, T cell receptor.

The receptors for IL-17 family cytokines are heterodimers consisting of two subunits; several IL-17R subunits are redundantly used as a component of multiple IL-17R dimers (1–3). IL-17 family cytokines and their receptors are summarized in Table 1. The receptor for IL-17A consists of IL-17RA and IL-17RC subunits. The IL-17RA molecule is also a subunit of receptors for IL-17C, IL-17E and IL-17F. In early studies, IL-17RA (or IL-17R)-deficient mice were used as a murine model that lacks IL-17A function; however, IL-17RA-deficiency confers inability to respond to not only IL-17A but also to IL-17C, IL-17E and IL-17F. Therefore, careful re-evaluation of early reports using IL-17RA-deficient mice is required. IL-17RB and IL-17RC subunits are also used as subunits of receptors for multiple IL-17 family cytokines: IL-17RB is used for IL-17B and IL-17E, and IL-17RC for IL-17A and IL-17F. Activation signals delivered from the IL-17Rs are summarized in recent reviews (2.3).

IL-17 family cytokines induce inflammatory responses via activation of their receptors. Receptors for IL-17A are expressed by various cells, including epithelial and endothelial cells and fibroblasts (1–3); IL-17A stimulation inducing production of AMPs and pro-inflammatory cytokines. AMPs, which comprise various molecules such as β-defensins and S100A8/A9 (1, 4, 5), are produced to kill pathogens, especially bacteria and fungi. The pro-inflammatory cytokines include granulocyte-colony stimulating factor, which activates neutrophil production in the bone marrow, and chemokines which induce neutrophil migration. IL-17F shares receptors with IL-17A, and induces responses just as IL-17A does. The functions of other IL-17 family cytokines have been demonstrated recently, as discussed in this review, in which we summarize the roles of hematopoietic cell-derived IL-17A and non-hematopoietic cell-derived IL-17 family cytokines in immune response to various pathogens and discuss our recent observations on the functional differences between the two categories of IL-17s.

Table 1. IL-17 family cytokines and their receptors

Cytokine	Receptor subunits	
IL-17A	IL-17RA	IL-17RC
IL-17B	?	IL-17RB
IL-17C	IL-17RA	IL-17RE
IL-17D	?	?
IL-17E	IL-17RA	IL-17RB
IL-17F	IL-17RA	IL-17RC
IL-17A/F	IL-17RA	IL-17RC

IL-17A/F indicates heterodimer of IL-17A and IL-17F.

ROLE OF HEMATOPOIETIC CELL-DERIVED IL-17A IN INFECTIONS

IL-17A is produced mainly by lymphoid cells, including Th17, Tc17 and γδ T cells, and ILC3, in the course of various infections. Several pathogens also induce IL-17A production by neutrophils. In this part of the review, we summarize the role of hematopoietic cell-derived L-17A in infections.

Extracellular bacterial infections and IL-17A

Involvement of IL-17A in infections was first reported in a *Klebsiella pneumoniae* lung infection mouse model. IL-17RA-deficient mice with pulmonary infection with extracellular bacteria *K. pneumoniae* have shorter survival, weaker neutrophil induction and greater bacterial burdens in the lung and spleen than infected wild type mice from an early stage of infection, such as Day 2 (18). Because IL-17A production of CD4+ and CD8+ T cells has been detected (19), Th17 and Tc17 are considered the IL-17A-producing cells in these infections. IL-17A production from Day 2 post infection indicates that the T cells are not *Klebsiella* antigen-specific T cells but innate type T cells that can respond to infection in the absence of antigen-specific receptors such as natural Th17 (nTh17) (20). Recent reports have shown that *K. pneumoniae* lung infection induces IL-17A production not only by CD4+T cells, but also by innate lymphocytes including γδT cells, invariant NKT cells, TCRαβ+CD4-CD8- T cells (21) and ILC3 (22). The mechanism of IL-17A-dependent protection against *K. pneumoniae* has been attributed to neutrophils induced by IL-17A because there are significantly fewer neutrophils in bronchoalveolar lavage fluid in the infected lungs of IL-17RA-deficient mice than in those of wild type mice (18). However, a recent study showed that protection against *K. pneumoniae* infection in the lung does not depend on neutrophils but on IL-17A-activated inflammatory macrophages (22), which also show enhanced bactericidal activity with increased production of reactive oxygen species (22).

IL-17A is also induced by infections with other extracellular bacteria, including *Staphylococcus aureus* (23–25), *Pseudomonas aeruginosa* (26, 27), *Bordetella pertussis* (28–30), *Escherichia coli* (31), *Citrobacter rodentium* (32, 33), *Yersinia pestis* (34) and *Helicobacter pylori* (35, 36). In many of these infections γδ T cells are the major IL-17A-producing cells (9). In *S. aureus* lung and skin infections (23, 24), *E. coli* peritoneal infection (31), and even colonization of the eyes by commensal *Corynebacterium* (37), the major IL-17A-producing cells are γδ T cells in mice; these cells enhance

protective immunity to these pathogens. Although the precise mechanism of IL-17A-dependent protective responses has not been identified, this protection is correlated with induction of neutrophils and expression of chemokines and AMPs (23, 24, 31, 37). In contrast, in a cecal ligation and puncture model of murine sepsis, γδ T cell-derived IL-17A enhances lethality, possibly through increased release of pro-inflammatory cytokines in sera (38). Therefore, IL-17A from the same cells could have both protective and exacerbating roles in infections: the former through induction of anti-microbial effectors such as neutrophils and AMPs to eliminate pathogens, and the latter through induction of excess inflammatory responses and tissue damage.

B. pertussis infection also induces IL-17A-producing γδ T cells at an early stage of infection; however, Th17 becomes detectable at a later stage (30). Non-viable bacterial components can induce IL-17A production: *B. pertussis* acellular vaccine (29) and pertussis toxin alone (28) can induce Th17. Therefore, pertussis toxin may serve as an adjuvant for inducing Th17 cells. This activity has been empirically used to induce a Th17-dependent experimental autoimmune model. Pertussis toxin has been inoculated after immunization with a myelin-specific myelin oligodendrocyte glycoprotein peptide to induce experimental autoimmune encephalomyelitis, a murine model of multiple sclerosis; the supplementation with pertussis toxin skewing myelin oligodendrocyte glycoprotein-specific immune responses to Th17 type (39).

Intestinal bacterial infections tend to induce Th17 cells against pathogens. *C. rodentium* intestinal infection of mice induces Th17 in the lamina propria of the colon (32). However, IL-17A is dispensable to protective immunity and immunopathology of such infection because IL-17RC-deficient mice, which lack receptors for IL-17A, have a survival rate and histological changes similar to those of wild type mice after *C. rodentium* intestinal infection (33). *H. pylori* gastric infection of humans also induces Th17 (35) and culture of *H. pylori*-infected gastric epithelial cells in the presence of IL-17A and with another Th17-derived cytokine, IL-22, enhances bacterial elimination, which correlates with expression of AMPs (36).

Chronic pulmonary infection with *P. aeruginosa,* which frequently occurs in patients with cystic fibrosis, induces IL-17A production (26) and a murine model of chronic *P. aeruginosa* infection shows that IL-17A produced by Th17, γδ T cells and ILC3 plays a protective role (27). Given that IL-17A is important in other pneumonia models of *K. pneumoniae* and *S. aureus* infections (18, 23–25), IL-17A must have a pivotal role in optimal control of extracellular bacteria in the lung.

IL-17A also plays an important role in oral mucosa with periodontitis. *Porphyromonas gingivalis,* a causative pathogen of periodontitis, induces IL-17A expression and IL-17RA-deficient mice reportedly develop more severe periodontitis (40), indicating IL-17A plays a protective role against periodontitis. However, another study found that IL-17A concentrations correlate with the severity of periodontitis (41). These results are a reminder that excess inflammatory responses induced by IL-17A can induce tissue damage and may have disadvantages for the host in elimination of pathogens.

Although the vast majority of studies on IL-17A have demonstrated that lymphoid cells produce cytokines, one study has shown that *Yersinia pestis* infection induces IL-17A production by neutrophils and that *Y. pestis*-induced IL-17A participates in protective immunity (34). Given that IL-17A production by neutrophils has also been reported in *Legionella* and fungal infections (42, 43), we may have to re-evaluate the role of IL-17A produced by non-lymphoid hematopoietic cells.

The mechanism of hematopoietic cell-derived IL-17A-dependent protective responses to extracellular bacteria is summarized in Figure 1a.

Intracellular bacterial infections and IL-17A

A protective role of IL-17A in infections by intracellular bacteria was first reported for *Listeria monocytogenes* infection in mice (44, 45). IL-17A produced by γδ T cells reportedly has a pivotal role in early protection against *L. monocytogenes* infection before establishment of acquired Th1 and Tc1 immune responses. *L. monocytogenes*-induced γδ T cells express a restricted TCR Vγ repertoire, Vγ4 and Vγ6 (45), which is identical to that of the IL-17A-producing γδ T cells in various systems (9). Although IL-17A induces expression of AMPs in *L. monocytogenes* infection (45), the protective mechanism of IL-17A at an early stage of infection is still unclear. Culture of *L. monocytogenes*-infected hepatocytes in the presence of IL-17A with another Th17-derived cytokine, IL-22, reportedly induces expression of phospholipase A2 group IIA, a bactericidal phospholipase which internalizes and co-localizes with intracellular *L. monocytogenes*. Given that phospholipase A2 group IIA kills *L. monocytogenes in vitro*, it may participate in IL-17A-dependent protection against *L. monocytogenes* in hepatocytes (46). *L. monocytogenes* infection also enhances induction of protective acquired immunity through promoting cross-presentation for CD8+T cell induction (47). Interestingly, non-human primate Rhesus macaques, which use γδ TCR with high homology with humans, also produce IL-17A after *L. monocytogenes* infection (48). Therefore, it is highly

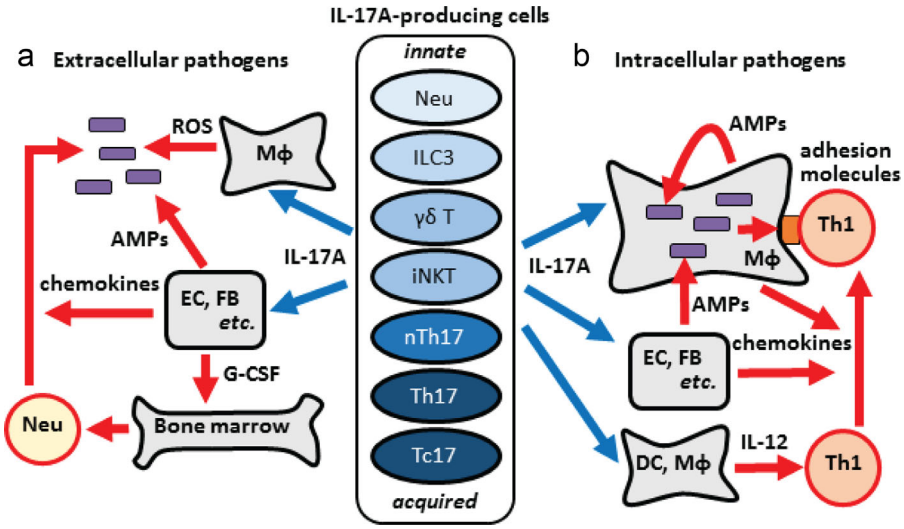

Figure 1. Mechanism of IL-17A-dependent protective immunity against (a) extracellular and (b) intracellular bacteria. IL-17A is produced by various hematopoietic cells of innate and acquired immunity in the course of bacterial infections, as mentioned in the text. IL-17A induces various immune effectors (indicated by red arrows) and induces inflammatory responses to eliminate the pathogens. EC, epithelial cells; FB, fibroblasts; Mϕ, macrophages; Neu, neutrophils.

possible that IL-17A-producing γδ T cells participate in immune responses to *L. monocytogenes* infections in humans.

IL-17A also has an important role in optimal protective immunity to *Mycobacterium tuberculosis*, the causative pathogen of tuberculosis. *M. tuberculosis* is an intracellular bacterium that mainly infects macrophages in infected organs such as the lung. It is well established that IFN-γ produced by Th1 has a primary role in protective immunity. Lung infection with *M. tuberculosis* (49) or *Mycobacterium bovis* BCG (50) induces IL-17A-producing γδ T cells in the lung. It has been demonstrated that IL-17A-deficient mice show reduced protection to pulmonary *M. tuberculosis* infection (51–53). Mycobacterial Ag-specific Th1 response was normal in IL-17A-deficient mice in one study (52), whereas decreased expression of IFN-γ was demonstrated in other study (53). Given that granuloma formation induced by mycobacterial infection is less pronounced in the absence of IL-17A and this correlates with weaker expression of adhesion molecules (50, 51), it has been proposed that IL-17A enhances establishment of mature granulomas through induction of adhesion molecules, which are required for tight interactions between infected macrophages and Th1. Defective mature granuloma formation may result in the weaker protective immunity to *M. tuberculosis* in IL-17A-deficient mice. In contrast, several studies have shown that IL-17A is dispensable in protective immunity to *M. tuberculosis*. IL-17A-deficient mice infected with a laboratory strain of *M. tuberculosis* showed normal bacterial burdens; however, the same study showed that infection with a clinically isolated virulent *M. tuberculosis* strain resulted in increased bacterial burdens in IL-17A-deficient mice (54). Furthermore, bacterial burdens in anti-IL-17A antibody-treated mice are similar to those of control antibody-treated mice after *M. tuberculosis* lung infection (55). IL-17RA-deficient mice also show normal protective responses to *M. tuberculosis* infection (55, 56). The reason for these discrepancies in the role of IL-17A in *M. tuberculosis* infections requires further clarification.

Another set of studies has indicated a protective role for IL-17A in vaccine-induced immunity to *M. tuberculosis*. A vaccination protocol that induces mycobacterial antigen-specific Th17 with Th1 is effective in protecting mice from *M. tuberculosis* challenge infection in a IFN-γ- and IL-17A-dependent manner (57); these authors proposed that IL-17A from Th17 induces Th1 in the infected lung. Another vaccine protocol that induces mycobacterial Ag-specific Th17 in the lung by intranasal administration of an mycobacterial antigen with a mucosal adjuvant cholera toxin reportedly induces migration of BCG-induced protective Th1 cells into the lung (58). These results suggest that Th17 has a protective role in pulmonary tuberculosis. However, excess induction of mycobacterial antigen-specific Th17 injures *M. tuberculosis*-infected lungs (59). Therefore, induction of optimal activity of IL-17A-producing cells is required to control pulmonary tuberculosis.

IL-17A has a protective role in mycobacterial infections in humans. In RORγt-deficient patients,

expression of IL-17A and other Type 3 cytokines (IL-17F and IL-22) by T cells is not induced and they develop mycobacterial infections after inoculation with a low-virulent *M. bovis* BCG vaccine strain, suggesting high susceptibility to mycobacterial infection in the absence of IL-17A (60). Furthermore, healthy individuals in contact with patients with tuberculosis show strong mycobacterial antigen-specific Th17 responses whereas patients with tuberculosis show weak Th17 responses (61). The results suggest that Th17 is correlated with control of *M. tuberculosis*.

IL-17A induction has also been reported in infections by other intracellular bacteria, *Francicella tularensis* (62), *Legionella pneumophila* (42), *Chlamidia muridarum* (42, 63, 64) and *Mycoplasma pneumoniae* (65). IL-17A produced by Th17 and γδ T cells in *F. tularensis* infection activates DCs and macrophages to produce IL-12, which results in enhanced production of protective IFN-γ (62). IL-17A produced in *L. pneumophila* (42) and *C. muridarum* (63, 64) also enhances IFN-γ production. Interestingly, the IL-17A-producing cells in *L. pneumophila*-infected mice are neutrophils rather than lymphoid cells. We may have to re-evaluate the importance of non-lymphoid hematopoietic cell-derived IL-17A in intracellular bacterial infections.

The mechanism of IL-17A-dependent protective responses to intracellular bacteria is summarized in Figure 1b.

Fungal infections and IL-17A

It has been reported that infection with fungi such as *Candida albicans* induces fungal antigen-specific Th17. IL-23 produced by DCs has a pivotal role in that induction (66), whereas C-type lectin receptors dectin-1 and dectin-2 expressed on DCs, which recognize fungal β-glucan (67) and α-mannan (68), respectively, play roles in induction of IL-23 production. The IL-17A produced by fungal antigen-specific Th17 cells is pivotal in protective immunity against systemic and mucosal *C. albicans* infections. IL-17RA-deficient mice and dectin-2-deficient mice are both susceptible to systemic infection with *C. albicans* (68, 69). In oropharyngeal candidiasis of mice, IL-17A is produced by γδ T and nTh17 cells at an early stage of infection and has a pivotal role in protective immunity (70). Interestingly, IL-17A-induced protection does not depend on neutrophils (71) but on AMPs such as β-defensins (72). Commensal *Corynebacterium*-induced IL-17A-producing γδ T cells also reportedly have an important role in early protection against *C. albicans* ocular infection. All these findings indicate that innate and acquired IL-17A-producing lymphocytes are important anti-fungal effector cells.

IL-17A-dependent immunity to *C. albicans* has also been detected in humans. Individuals with mutations in RORγt, and IL-17RA have a high incidence of mucocutaneous candidiasis (60, 73, 74), as do those with mutations of CARD9, an adaptor protein essential for signal transduction of dectin-1 and dectin-2 and induction of Th17 response against *C. albicans* (75). In the latter group, the mucocutaneous candidiasis is accompanied by a weak Th17 response (76). Furthermore, some patients with ankylosing spondylitis have reportedly developed candidiasis after receiving an anti-IL-17A mAb (secukinumab) (77). Therefore, defects in the IL-17A–IL-17RA/IL-17RC axis are candidates for contributing to repeated or chronic candidiasis.

Fungal infections other than candidiasis have also been reported to induce IL-17A production. Infection of mice with *Cryptotoccus neoformans* induces IL-17A production and the importance of the IL-17A is suggested in IL-23-deficient or IL-17RA-deficient mice (78, 79). *Pneumocystis carinii*-infected mice show IL-17A dependent protection, which is impaired in IL-23-deficient mice (80). These reports demonstrate that IL-17A has a protective role against fungal infections. In contrast, IL-17A produced by *Aspergillus* or *Fusarium* conidial infections of lung induces tissue damage via recruitment of neutrophils or eosinophils (43, 81). Given that excess activation of Th17 cells can result in inflammatory tissue injury at the site of activation, Th17 responses to fungal infections should be carefully controlled.

Parasitic infections and IL-17A

There have been several reports of induction of IL-17A expression in infections with parasites, including protozoa and helminths. IL-17A induced in *Trypanosoma cruzi* infection has been shown to activate macrophages to internalize and kill these protozoa (82). Interestingly, the IL-17A-producing cells that are activated by trans-sialidase of *T. cruzi* are B cells (83). *Acanthoamoeba castelli* causes keratitis of the cornea and protective immunity against this infection depends on IL-17A produced by Th17 (84). *Leishmania* (85, 86) and *Toxoplasma gondii* (87, 88) also induce expression of IL-17A, the role of which is still unclear because both protective and non-protective roles have been reported. *Schistosoma* helminths, which cause liver granulomas and fibrosis, also induce IL-17A production by Th17 and γδ T cells (89–91). Lack of IL-17A or IL-23 results in decreased granuloma formation and suppression of liver fibrosis, indicating that IL-17A can exacerbate clinical symptoms of schistosomiasis.

Viral infections and IL-17A

IL-17A plays both protective and detrimental roles in viral infections. Influenza virus infection induces IL-17A expression (92–95) and IL-17A-deficient mice have lower survival rates and increased virus titers, suggesting that IL-17A has a protective role against this virus. IL-17A reportedly induces recruitment of CXCR5+ B cells into infected lung (93); however, the significance of IL-17A-dependent B cell responses in elimination of influenza viruses is yet to be determined. In contrast, another study demonstrated that IL-17RA-deficient mice have higher survival rates after influenza virus infection than wild type mice (95). Corneal damage in herpes simplex virus-1-infected mice is also ameliorated by anti-IL-17A antibody treatment or deficiency of IL-17RA (96). These reports suggest that IL-17A produced in viral infections can enhance tissue destruction by inflammation. Thus, production of optimal amounts of IL-17A can be beneficial whereas excess IL-17A induces harmful tissue damage in the course of viral infections.

ROLE OF NON-HEMATOPOIETIC CELL-DERIVED IL-17 FAMILY CYTOKINES IN INFECTIONS

IL-17B, IL-17C and IL-17D are expressed by non-hematopoietic cells such as epithelial cells (11–14). Although IL-17E and IL-17F were originally identified as T cell-derived cytokines, recent studies have demonstrated that epithelial cells produce these cytokines (14–17). Here, we would like to summarize recent reports showing the importance of non-hematopoietic cell-derived IL-17s in immunity to infections.

IL-17C

IL-17C is produced by various epithelial cells, including intestinal and tracheal epithelial cells and keratinocytes, and its receptor IL-17RA/IL-17RE complex is also expressed by epithelial cells (11), indicating that IL-17C is an autocrine cytokine of epithelial cells. Stimulation of epithelial cells with *E. coli* or pathogen-associated molecular patterns, including bacterial peptidoglycan and flagellin, induces IL-17C production, which activates expression of chemokines, AMPs, granulocyte-colony stimulating factor and IL-1β by epithelial cells (11). IL-17C also enhances expression of tight junction molecules occluding, claudin-1 and claudin-4 on intestinal epithelial cells (97). With all these functions, the IL-17C–IL-17RA/IL-17RE axis enhances immunological and physiological barrier functions against invasion of pathogens (Fig. 2a). In mice with *C. rodentium* intestinal infection, IL-17C is produced by colonic epithelial cells, which in turn produce AMPs in response to IL-17C (12). IL-17RE-deficient mice show decreased production of AMPs after *C. rodentium* infection, which results in increased bacterial burdens and decreased survival rates (12), clearly demonstrating the protective role of the IL-17C–IL-17RA/IL-17RE axis against these infections. *C. albicans* (98, 99), *S. aureus* (100),

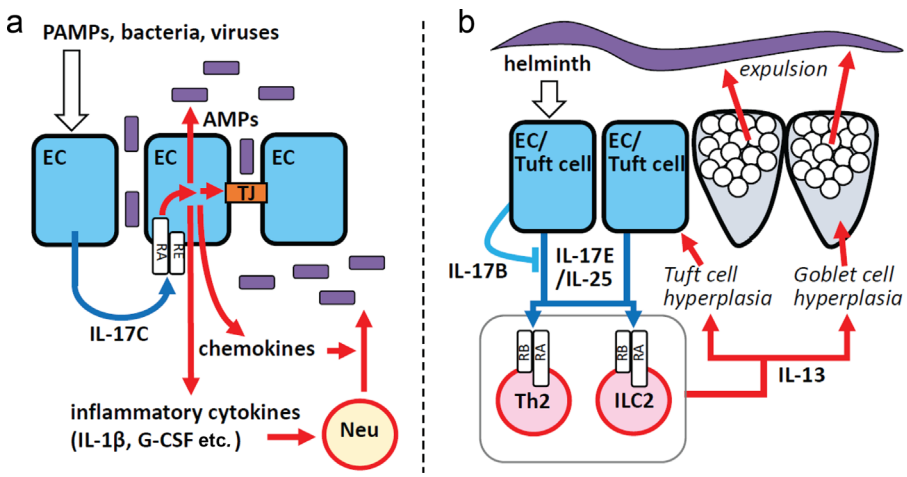

Figure 2. Role of epithelial cell-derived IL-17s in protection against infections. (a) IL-17C produced by epithelial cells in response to bacteria, fungi, viruses and pathogen-associated molecular patterns activates epithelial cells in an autocrine fashion, inducing production of AMPs and inflammatory cytokines, which promotes generation and migration of neutrophils. IL-17C also induces expression of tight junction molecules to enhance physiological barrier in intestinal epithelia. (b) IL-17E production of epithelial tuft cells is induced by helminth infections; L-17E stimulates ILC2 and Th2 to produce IL-13. IL-13 induces hyperplasia of tuft and goblet cells and goblet cells induce expulsion of the parasites. IL-17B derived from epithelial cells suppresses the function of IL-17E. EC, epithelial cell; Neu, neutrophils; PAMP, pathogen-associated molecular pattern; TJ, tight junction.

H. pylori (101), *P. aeruginosa* (102) and herpes simplex virus (103) also induce IL-17C production by epithelial cells. Interestingly, *P. aeruginosa*-induced IL-17C expression by lung epithelial cells in mice with pulmonary infections depends on the presence of IL-17A (102), suggesting the existence of a network of IL-17 family cytokines that regulate expression of each of its members.

IL-17E

IL-17E was originally identified as IL-25 from Th2 cells and was later classified as a member of the IL-17 family of cytokines. IL-17E uses IL-17RA/IL-17RB complex as its receptor (10). IL-17E is produced not only by Th2 cells, but also by mast cells, eosinophils, basophil, and alveolar macrophages; all of these cell sources are involved in allergic responses (10).

Interestingly, IL-17E is also produced by specialized intestinal epithelial cells called tuft cells (15, 16), which constitutively produce IL-17E to maintain homeostasis of ILC2s. After infection with the intestinal nematode *Nippostrongylus brasiliensis*, IL-17E production of tuft cells increases, resulting in activation of ILC2 and Th2 to produce IL-13. In turn, IL-13 induces hyperplasia of goblet cells and tuft cells themselves, enhancing expulsion of this worm by goblet cells. In contrast, IL-17E suppresses protection against bacterial infection. *C. rodentium* intestinal infection induces IL-17E expression whereas IL-17E-deficient mice show lower bacterial burdens than wild type mice (13). Therefore, IL-17E produced by epithelial cells enhances Type 2 immunity and is accordingly protective against parasites but suppresses protection against bacterial infections (Fig. 2b).

IL-17B

IL-17B is another epithelia-derived IL-17 family cytokine. IL-17B shares the receptor IL-17RB with IL-17E (2–3) and suppresses IL-17E-induced IL-6 production by colon epithelial cells (13). In *C. rodentium* intestinal infection, IL-17E-deficient mice show fewer, whereas IL-17B-deficient mice show more numerous *C. rodintium* than wild type mice. Additionally, IL-17B/IL-17E-double deficient mice show the same numbers of *C. rodintium* as wild type mice (13), indicating that IL-17E-mediated suppression of protective immunity to *C. rodintium* in the intestine is counteracted by IL-17B, possibly through competitive binding of IL-17B to IL-17RA/IL-17RB complex (Fig. 2b).

IL-17D

The function(s) and receptor for IL-17D are still unclear but one study demonstrated IL-17D production by fibroblasts in immune responses to infections with vaccinia virus and mouse cytomegalovirus (14). The infections were more severe in the absence of IL-17D. Given that IL-17D expression is induced by the oxidative stress sensor Nrf2 (14, 104), infections that induce oxidative stress may induce IL-17D expression. Further analyses are required to address the issue.

IL-17F

IL-17F was originally identified as a Th17-derived cytokine (105). However, IL-17F is also expressed in Rag2-deficient mice, which lack T and B cells, and by intestinal epithelial cells (17). Furthermore, IL-17F-deficient mice are susceptible to intestinal *C. rodintium* and nasal *S. aureus* infections (17). All published findings suggest that IL-17F is produced by epithelial cells and participates in mucosal immunity to infections.

We have also identified a role of IL-17F in the lungs of *Mycobacterium*-infected mice (Umemura et al., 2017, submitted). We found that IL-17F-deficent mice show increased bacterial burdens in *M. tuberculosis*-infected lungs, whereas we did not detect IL-17F production in lymphoid and other hematopoietic cells. Histological examination revealed that IL-17F is expressed by Type II alveolar epithelial cells even before infection. IL-17F expression accumulates in Type II alveolar epithelial cells at the site of infection in mycobacteria-infected lungs. Therefore, we hypothesize that IL-17A-producing γδ T cells, which migrate into granulomas, support granuloma maturation from within those granulomas, whereas IL-17F-producing alveolar epithelial cells, which wrap around granulomas, support protective immunity from outside those granulomas (Fig. 3a).

Epithelial cell-derived and hematopoietic cell-derived IL-17s may have complementary functions, as illustrated in Figure 3b and c. In the immediate early stage of epithelial infections, IL-17C and IL-17F produced by epithelial cells moderately activate epithelial cells at epithelial sites of infection to enhance their barrier functions against bacterial and fungal pathogens (Fig. 3b). At a later stage of these infections, Th17 and other IL-17A-producing leukocytes strongly activate epithelial cells to enhance barriers to migration, accumulation in the infected sites and production of large amounts of IL-17A (Fig. 3c). In the case of helminth infection, epithelia-derived IL-17E and Th2-derived IL-17E are involved in immediate early and later stages of protection, respectively, at the site of infected epithelia.

Concluding remarks

IL-17 family cytokines are important regulators of inflammatory responses and participate in immune

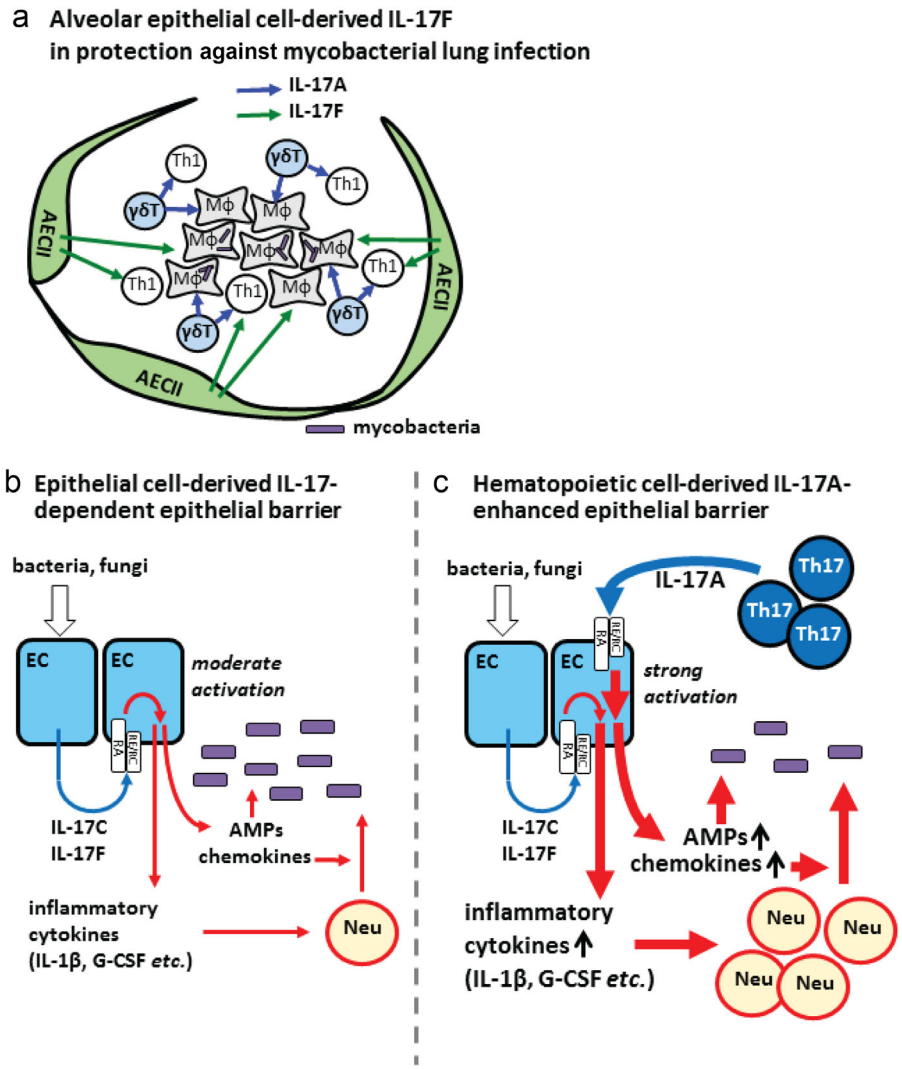

Figure 3. Co-operation of hematopoietic cell-derived IL-17A and epithelial cell-derived IL-17C/IL-17F. (a). In the mycobacteria-infected lung, both γδ T cell-derived IL-17A and type II alveolar epithelial cell (AECII)-derived IL-17F co-operatively participate in protective immunity against the infection; however, the precise mechanism of this protection has not yet been clearly established. (b) Epithelial cells produce IL-17C or IL-17F at the immediate early stage of epithelial infections. The epithelial cells are activated by the IL-17s in an autocrine manner and produce AMPs and inflammatory cytokines. (c) In the course of epithelial infection, innate IL-17A-producing cells (ILC3, γδ T cells, nTh17 etc.) migrate into the site of infection at an early stage and strengthen protective responses by IL-17 family cytokines through enhancement of AMPs production and inflammatory responses. At a later stage of the infection, Th17 cells also participate in the response.

responses to infections. Recent reports have revealed new roles for IL-17A, the best characterized of this family, in infections. Functions of IL-17 family cytokines other than IL-17A have also recently been reported. Expression of IL-17 family cytokines is not restricted to hematopoietic cells: non-hematopoietic cell-derived IL-17s, especially those from epithelial cells, are important in protection at sites of infected epithelia. We must therefore consider where and by which cells the IL-17 family cytokines are produced to understand their *in vivo* functions.

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DISCLOSURE

The authors have no conflicts of interest to declare.

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