REVIEW

The roles and functional mechanisms of interleukin-17 family cytokines in mucosal immunity

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The mucosal immune system serves as our front-line defense against pathogens. It also tightly maintains immune tolerance to self-symbiotic bacteria, which are usually called commensals. Sensing both types of microorganisms is modulated by signalling primarily through various pattern-recognition receptors (PRRs) on barrier epithelial cells or immune cells. After sensing, proinflammatory molecules such as cytokines are released by these cells to mediate either defensive or tolerant responses. The interleukin-17 (IL-17) family members belong to a newly characterized cytokine subset that is critical for the maintenance of mucosal homeostasis. In this review, we will summarize recent progress on the diverse functions and signals of this family of cytokines at different mucosal edges.

Cellular & Molecular Immunology (2016) 13, 418–431; doi:10.1038/cmi.2015.105; published online 28 March 2016

Keywords: IL-17 family cytokines; mucosal immunity; signal transduction

INTRODUCTION

Our body constantly encounters various microbial insults at different mucosal surfaces (that is, intestine, skin and lung). Although they are anatomically distinct from one another, our mucosal surveillance systems share a simple pattern of microbial recognition and subsequent immune responses. Microbes can be recognized by these systems either structurally or functionally.¹ The innate mucosal immune system detects microorganisms by recognizing their conserved features. These conserved structures (that is, bacterial cell wall components or viral nucleic acids) are detected as microbial-associated molecular patterns (MAMPs) by several types of host pattern-recognition receptors (PRRs) at different levels. The PRRs include Toll-like receptors (TLRs), Nod-like receptors (NLRs), RIG-I-like receptors (RLRs), C-type lectin receptors (CLRs), AIM2-like receptors (ALRs), and the newly identified cyclic GMP–AMP synthase.^{2–4} In addition to their structural diversity, PRRs are assembled at distinct subcellular or cellular locations and thus sense different types of bacteria, fungi and viruses.¹ The recognition signals triggered by PRRs instruct the adaptive immune system response by determining the type of invasion.

Commonly, the tightly connected epithelial layer and the intraepithelial phagocytes distributed in the layer constitute the first line of detection and defense of the mucosal surveillance system.^{1,5} The epithelial layer functions not only as a physical but also as a biochemical barrier for various microorganisms. In the intestine, specialized epithelial cells in the layer [that is, Paneth cells and goblet cells that constantly express specific antimicrobial peptides (AMPs) and mucins, respectively] maintain commensals in a steady state and prevent pathogen invasion. Intestinal epithelial cells also help lamina propria resident plasma cells transport IgA molecules into the intestinal lumen to maintain intestinal homeostasis.⁵ Once the epithelium is breached, invasive microbes may cross the layer and reach the basolateral surface of the epithelial cells, where they will be detected by a set of distinct TLRs, such as TLR2, TLR3, TLR4 and TLR5. Once activated, epithelial cells are ready to trigger an innate immune response by releasing chemokines and cytokines to recruit circulating immune cells.⁵ Epithelial cells may also immediately respond to microbial puncture by directly expressing antimicrobial peptides.⁵ In addition, epithelial cells can release tissue repair-related cytokines to resolve mucosal damage and stress.⁵ Intraepithelial

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Received: 18 October 2015; Revised: 21 November 2015; Accepted: 21 November 2015; published online 28 March 2016

Figure 1 Overview of the interleukin-17 family of cytokines. The IL-17 family of cytokines includes six members (IL-17A to IL-17F), whereas the receptor family consists of five members (IL-17RA to IL-17RE). The most studied members (IL-17A and IL-17F) form a homodimer or heterodimer to bind to the IL-17RA and IL-17RC complex and trigger downstream signalling that activates the host defense and inflammatory responses. Although IL-17B binds to IL-17RB, the downstream signalling pathways of this pair has not been revealed. IL-17B antagonizes IL-17E-mediated functions by competitively binding to IL-17RB. IL-17C triggers downstream signalling for host defense and autoimmune inflammation by binding to the IL-17RA and IL-17RE complex. IL-17E associates with the IL-17RA and IL-17RB complex to activate Th2 responses. IL-17D may recruit NK cells to reject tumours. Neither the ligand for IL-17RD nor the receptor for IL-17D has been identified. Act1 may be a common receptor proximal adaptor for IL-17 family cytokine-mediated signalling.

phagocytes, which mainly consist of macrophages and dendritic cells, are also equipped with PRRs and have access to the lumen side of mucosal surfaces to detect commensals or pathogens and to present distinct antigens.¹ Once microbes spread from an epithelial breach, the subepithelium antigen-presenting cells (APCs) immediately detect them via PRRs and present antigens to resident T or B cells. Generally, the different recognition patterns of the innate immune system instruct the subsequent adaptive immune response by inducing the production of distinct cytokines.^{1,6} For instance, APCs produce IL-12 to promote a T helper 1 (Th1) response. Alternatively, these cells secrete IL-23 and IL-6 to induce Th17 cell differentiation. Epithelial cells produce TSLP, IL-33 and IL-17E (also known as IL-25) in response to helminths or allergens to induce Th2 immunity.¹ More recently, a previously uncharacterized innate cell type called innate lymphoid cells (ILCs) was shown to be controlled by these cytokines in a similar way.^{7,8} ILC1s, ILC2s, and ILC3s represent innate populations with developmental programming similar to the adaptive populations of Th1, Th2 and Th17 cells, respectively.^{7,8} Th1 cells and ILC1s can produce the effector cytokine IFN- γ to induce cytotoxicity in the host. Th2 cells and ILC2s secrete typical type 2 cytokines, such as IL-4, IL-5, IL-13, AREG and IL-9, to expulse worms and repair

tissue damage. Th17 cells and ILC3s release IL-17 and IL-22 as their signature cytokines to promote antimicrobial activity and the epithelial integrity of the host.

The induction and function of two IL-17 family cytokines (IL-17 and IL-17E) on mucosal surfaces have been extensively studied over the past decade.^{9,10} Recent progress has revealed that other less well-characterized family members (that is, IL-17C and IL-17B) are also essential for epithelial mucosal homeostasis. In this review, we will highlight the latest advances for this family of cytokines and especially their impacts on orchestrating either proper or aggressive mucosal immune responses.

OVERVIEW OF IL-17 FAMILY CYTOKINES

The IL-17 family of cytokines has a broad of influence on different inflammatory responses.⁹ The IL-17 family members have been linked to the pathogenesis of multiple autoimmune diseases and also have emerging roles in host defense, allergic responses, or even tumorigenesis at different mucosal boundaries (Figure 1).⁹

IL-17 (also called IL-17A) is the most studied member of this family. IL-17 was cloned from a T-cell hybridoma cDNA library in 1993.^{11,12} Soon after its discovery, IL-17 was found to

Figure 2 Functional roles of the Interleukin-17 family cytokines in mucosal immunity. Upon infection or tissue damage, pathogens, such as extracellular bacteria and fungi, or dysregulated commensals invade the epithelial barriers. The inflammatory microenvironments triggered by the invasions promote IL-17A and IL-17F production from ILC3s and Th17 cells. TLR signalling triggers IL-17C production in epithelial cells. IL-17A/F and other inflammatory cytokines also induce IL-17C production in these cells, whereas in turn IL-17C promotes IL-17A/F production in Th17 cells. IL-17C and IL-17A/F trigger host defenses and tissue repair responses in the epithelium. Conversely, parasites and allergens induce IL-17E production by epithelial or myeloid cells. Then, IL-17E targets Th2, Th9 or ILC2s to promote Th2-related responses. IL-17E also targets epithelial cells to produce inflammatory cytokines. Moreover, commensal-derived IL-17E inhibits Th1 and Th17 responses. Although the functional mechanisms are not fully understood, IL-17B and IL-17E appear to have opposing functions.

be a hallmark cytokine released by T-helper 17 (Th17) cells; its expression was controlled by the transcription factor ROR γ t.¹³ Recently, other studies have shown that a broad range of innate immune cells, including $\gamma\delta$ T cells, several subtypes of type 3 innate lymphoid cells (ILC3s), natural killer (NK) cells, invariant NK T (iNKT) cells and neutrophils, can rapidly produce IL-17 during the early stage of the immune responses.¹⁴ IL-17 activates the NF- κ B, MAPKs and C/EBP cascades to induce proinflammatory cytokine, chemokine, antimicrobial peptide and matrix metalloproteinase production with different inflammatory contents.¹² IL-17 also cooperates with TNF α or IL-22 to stabilize chemokine gene messenger RNA (mRNA) expression or to amplify antimicrobial peptide production.¹² The IL-17 receptor complex, which consists of IL-17RA and IL-17RC, activates downstream signaling pathways by recruiting an adaptor molecule named Act1 (NF- κ B activator 1).¹² The following studies show that Act1 is not only the master mediator for IL-17 signaling but also a common signaling adaptor shared by other members of this family.⁹

On the basis of bioinformatics analysis of structural similarity, the cytokine family contains six members [IL-17, IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25) and IL-17F].¹⁵ IL-17 shares 16 to 50% amino-acid sequence similarity with the other cytokines in this family. IL-17F is the most homologous with

nearly 50% amino-acid sequence identity to IL-17, whereas IL-17E is the most distinct with only 16% similarity to IL-17.¹⁶ Consistently, IL-17F also shares similar cellular sources and signaling pathways with IL-17. Evolutionarily, the carboxyl-terminal amino acids of this family are more conserved. Four of the five conserved cysteine residues in this terminus form a cysteine-knot structure similar to that of the TGF- β , NGF and BMP super-family members.^{17,18} Although they structurally resemble IL-17 and IL-17F, the other family members have unique cellular sources and induction patterns. In general, IL-17C (the newest identified cytokine in the family) is primarily produced by epithelial cells or specialized epithelial cells such as keratinocytes, and its expression is controlled by the transcription factor NF- κ B rather than ROR γ t. IL-17C mRNA is also found in endothelial cells and leukocytes, but the function of IL-17C in these cells is poorly understood.^{10,19} IL-17E-producing cells are more diverse than the cells that produce IL-17C and include Th2 cells, eosinophils, basophils, alveolar macrophages, microglia, IgE-activated mast cells, epithelial cells and endothelial cells.⁹ IL-17E-producing cells are related to type 2 immunity. Although ERK and P38 inhibitors suppressed the production of IL-17E by allergens, the transcriptional mechanisms of IL-17E production during type 2 responses need to be elucidated.²⁰ IL-17B is highly

expressed in chondrocytes, intestinal epithelial cells, neurons, and breast cancer cells, but the functional roles of IL-17B in these cells have not been fully explored (Figure 2).⁹

The IL-17 receptor family contains five members based on EST database searches: IL-17RA (also known as IL-17R), IL-17RB, IL-17RC, IL-17RD and IL-17RE.¹⁵ All members of this family contain two extracellular fibronectin III-like domains and an intracellular SEF/IL-17R (SEFIR) domain.¹⁵ IL-17RA (the fundamental receptor family member) is believed to be a commonly required receptor for this family.⁹ Other receptors form different heterodimeric complexes with IL-17RA to mediate the signaling pathways triggered by the different IL-17 family cytokines. To date, IL-17A and IL-17F have been shown to form either homodimers or heterodimers that can bind to the IL-17RA and IL-17RC receptor complex to activate downstream signaling cascades, whereas IL-17E is believed to signal through the IL-17RA and IL-17RB receptor complex to activate its downstream pathways.^{9,21–24} At present, the IL-17RA and IL-17RE heterodimer is considered the functional receptor for IL-17C.^{25–27} IL-17RB has also been suggested to be a receptor for IL-17B;^{28,29} however, evidence from genetic deficiency experiments is lacking for this receptor and ligand combination. Moreover, whether IL-17RA is required for the function of IL-17B is also unclear. The receptor for IL-17D had not been identified to date. Previous studies showed that IL-17RD (originally called Sef), which was the orphan receptor in this family, was a negative regulator for the suppression of growth factor-mediated MAPK pathway activation.³⁰ IL-17RD was recently suggested to be a positive component in IL-17 signaling and a negative suppressor for TLRs signaling.^{31–33} However, the detailed molecular mechanisms underlying the roles of IL-17RD in these pathways are unknown, and whether there is a functional ligand for IL-17RD remains an open question in this field.

Because IL-17RA is shared by this family, the specificity of the cytokines is likely determined by the second receptor of the heterodimer. In addition, the cellular sources for IL-17 family cytokines and their receptors are diverse, as we discuss below. Thus, the differences in the cytokine-receptor combination largely shape the functional diversity of this family of cytokines at distinct barrier surfaces.

IL-17 FAMILY CYTOKINE-MEDIATED SIGNALING PATHWAYS

IL-17 and IL-17F

As described above, IL-17 can induce NF- κ B, MAPK and C/EBP activation to upregulate the expression of pro-inflammatory cytokines and chemokines. Moreover, IL-17 post-transcriptionally stabilizes chemokine mRNAs induced by TNF α .³⁴ Upon IL-17 binding to the IL-17RA-IL-17RC heterodimeric receptor complex, the adaptor molecule Act1 is recruited by the IL-17Rs through the SEFIR-SEFIR domain interaction.^{35,36} Then, Act1 initiates the formation of the TAK1-IKKs complex by recruiting and ubiquitinating TRAF6 in a Lys63-dependent manner.³⁷ This TRAF6-dependent pathway requires Act1's U-box-like E3 ligase activity and is

critical for the activation of the IL-17-induced NF- κ B and JNK pathways.³⁷ However, TRAF6 is not required for the IL-17-induced mRNA stabilization pathway,³⁸ suggesting that TRAF6-independent pathways may exist. Indeed, Act1 alternatively induces the assembly of the TRAF2/TRAF5-SF2 complex that protects chemokine mRNA from cleavage by the mRNA-splicing factor SF2.³⁹ The inducible I κ B kinase IKKi (also known as IKK ϵ) is also required for this process through the phosphorylation of Act1 at serine 311.⁴⁰ A deficiency in IKKi leads to the disruption of the Act1-TRAF2-TRAF5 complex without affecting the binding of Act1 to TRAF6, indicating that these two pathways are independently generated.⁴⁰ Furthermore, the Act1-TRAF2-TRAF5 complex stabilizes the mRNA that dissociates from SF2 by recruiting and ubiquitinating the ARE-binding protein HuR.⁴¹ These two TRAF6-independent pathways are probably only functionally complementary because no interaction has been detected between HuR and SF2.⁴¹ More recently, researchers reported a novel Act1-TRAF4-MEKK3-ERK5 circuit in keratinocytes that was critical for skin cancer promotion.⁴² In addition to TRAF molecules, the study also showed that Act1 was associated with heat-shock protein 90 (hsp90) after IL-17 stimulation; this association was critical for IL-17-mediated signal activation.⁴³ Interestingly, the Act1 mutant D10N, which is associated with psoriasis, cannot bind to hsp90 and fails to initiate IL-17-induced downstream signaling.⁴³

In addition to the SEFIR domain, other studies have shown that the C-terminal region and 'TIR-like loop' (TILL) structure of IL-17RA, the cytosol tail region of IL-17RC, and the N-terminal domain of Act1 are critical for IL-17 signaling.⁹ A recent study showed that IL-17 activated the NF- κ B pathway by down regulating microRNA-23b (miR-23b) to release its suppression on TAB2 and TAB3 expression.⁴⁴ Other data suggested that IL-17 could induce JAK-STAT or JAK-PI3K activation, although the molecular mechanisms underlying this effect are unknown.⁹

Similar to IL-17, IL-17F also signals through the IL-17RA-IL-17RC receptor complex to activate downstream pathways. In contrast to IL-17, IL-17F binds to IL-17RC with higher affinity than IL-17RA.²¹ Although they differ in their receptor binding affinities, the inflammatory responses mediated by these two cytokines require either IL-17RA or IL-17RC.²¹ Similar to IL-17, IL-17F also recruits Act1 and TRAF6 to IL-17Rs and activates the NF- κ B, MAPKs and C/EBP pathways in different cell types.⁴⁵

Because IL-17 can strongly induce inflammatory responses, its signaling must be kept under tight control to avoid detrimental chronic inflammation. One early study suggested that IL-17 could induce the dual-phosphorylation of C/EBP β by activating the ERK and GSK3 β kinases to sequentially inhibit the IL-17-induced expression of proinflammatory genes.⁴⁶ Other studies showed that the TRAF family proteins TRAF3 and TRAF4 suppressed IL-17 signaling by disrupting IL-17R-Act1-TRAF6 or Act1-TRAF6 complex formation and consequently controlling the progression of experimental autoimmune encephalomyelitis (EAE) in mice.^{47,48} The

ubiquitin proteasome pathway is widely used for signaling desensitization by degrading key signaling molecules. As discussed above, the adaptor protein Act1 is the master molecule downstream of the IL-17Rs. A recent study demonstrated that the SCF^{βTrCP-1/2} E3 ubiquitin ligase complex was recruited to Act1 upon persistent IL-17 stimulation to degrade Act1 by Lys48-linked polyubiquitination.⁴⁹ Eventually, Act1 degradation eliminated IL-17 signaling and subsequently desensitized cells in response to IL-17.⁴⁹

Although IKKi is required by the IL-17-induced TRAF6-independent mRNA stabilization pathway to phosphorylate Act1 at serine 311, both the IKKi and TBK1 (TANK binding kinase 1) kinases phosphorylate Act1 on three other serine sites after IL-17 stimulation. Act1 phosphorylation of these sites blocks its interaction with TRAF6 and eventually inhibits IL-17-induced NF-κB activation.⁵⁰ Because Act1 is an E3 ligase for TRAF6 polyubiquitination, the reverse deubiquitination process may exist. Indeed, two deubiquitinating enzymes [DUB; the ubiquitin-specific protease USP25 and TNFAIP3 (also called A20)] were reported to be negative regulators of the IL-17-induced NF-κB cascade because they deubiquitinate TRAF6.^{51,52} In addition, USP25 directly removes TRAF5 ubiquitination and consequently erases the signals for the TRAF5-dependent mRNA stabilization pathways.⁵¹ More recently, a study showed that another DUB [MCPIP1 (also named Regnase-1)] served as a negative regulator of IL-17 signaling.⁵³ Unexpectedly, its endoribonuclease but not its deubiquitinase activity was required for the suppression of IL-17 signaling. Mechanically, MCPIP1 inhibits IL-17-mediated signaling and inflammation by degrading the *Il6*, *Nfkbiz*, *Il17ra* and *Il17rc* mRNAs.⁵³

IL-17B and IL-17E

IL-17RB (also designated IL-17BR or IL-17Rh1) is the receptor for IL-17E.²⁸ Despite its lower binding affinity compared with IL-17E, IL-17B has also been reported to be a ligand for IL-17RB.²⁸ As described above, IL-17E signals through the IL-17RB-IL-17RA complex. Indeed, both IL-17RA and IL-17RB are functionally required for its signaling.²⁴ Genetic alteration of either IL-17RA or IL-17RB abolishes IL-17E-mediated signaling and the downstream response.²⁴ Unlike IL-17, which targets a broad range of cell types, IL-17E prefers to target hematopoietic cells such as Th2, Th9 or NKT cells to induce the production of the Th2 cytokines IL-4, IL-5, IL-9 and IL-13.⁹ In addition to T cells, IL-17RB is also expressed on monocytes, type 2 cytokine-producing myeloid (T2M) cells and several populations of type 2 innate lymphoid cells including nuocytes, non-T/non-B (NBNT) cells, multipotent progenitor type2 (MMP^{type2}) cells and innate type2 helper (ih2) cells.⁹ Non-immune stromal cells such as intestinal and respiratory epithelial cells also respond to IL-17E stimulation.⁹ Similar to IL-17RA, IL-17RB harbours a conserved SEFIR domain in the intracellular region and can recruit Act1 via the SEFIR-SEFIR interaction upon IL-17E stimulation.⁵⁴ The conditional deletion of Act1 in epithelial cells and T cells blocks allergen-induced airway inflammation.^{55,56} Epithelial-

derived Act1 is also required for IL-17E-mediated parasite expulsion through the expansion of intestinal Lin[−]c-Kit⁺ immune cells.⁵⁷ Moreover, the adaptor protein TRAF6 is recruited by IL-17RB and mediates IL-17E-induced NF-κB activation.⁵⁸

Recently, IL-17RB was shown to recruit another TRAF molecule (TRAF4) in an Act1-dependent manner. Mechanistically, TRAF4 recruits the E3-ligase SMURF2 to degrade DAZAP2, which is an IL-17RB-inhibitory protein.⁵⁹ Alternatively, IL-17E can directly activate STAT5 in an Act1-independent manner.⁶⁰ STAT5 is recruited to IL-17RB through unique tyrosine residues on the receptor after IL-17E stimulation.⁶⁰ Conditional depletion of STAT5 in T cells or epithelial cells causes a blunted IL-17E-mediated Th2 response.⁶⁰

Compared with IL-17E, IL-17B binds to IL-17RB with much lower affinity and the downstream signaling pathways of this pair need to be addressed. IL-17B was reported to induce the expression of the inflammatory cytokines TNFα and IL-1β in the monocytic THP1 cell line and to promote pathogenesis in a collagen-induced arthritis (CIA) mouse model when it was overexpressed in adoptively transferred T cells.⁶¹ In addition to promoting immune inflammation, several studies have shown that the IL-17B-IL-17RB axis enhances breast or pancreatic cancer progression by inducing the expression of inflammatory or survival genes in different tumor cells.^{62,63} Using an ectopic expression system, the authors demonstrated that the Act1-TRAF6-TAK1 complex was recruited by these processes.⁶² Because IL-17RB is highly expressed in breast and pancreatic tumors, these tumor cells may also respond to IL-17E. Surprisingly, instead of promoting tumor progression, IL-17E-induced tumor cell apoptosis by directly recruiting the TRADD-FADD-caspases complex to IL-17RB.⁶⁴ Thus, IL-17E acts antagonistically to IL-17B during tumor progression by inducing apoptosis in tumor cells. Recently, one study showed that IL-17B antagonized IL-17E-mediated inflammatory gene expression during colitis by inhibiting the binding of IL-17E to its receptor.⁶⁵ Although IL-17E and IL-17B bind to the same receptor, these two cytokines seem to antagonize one another through different mechanisms. The detailed signaling events mediated by these two cytokines (especially IL-17B) need to be addressed in future studies.

IL-17C

Similar to IL-17B, IL-17C can induce the expression of TNFα and IL-1β in human THP1 cells and mouse peritoneal immune cells.^{61,66} The ectopic expression of IL-17C *in vivo* by different methodologies also causes inflammatory responses in the lungs, joints and skin.^{19,61,67} Mechanistically, IL-17C binds to the IL-17RE-IL-17RA receptor complex to induce downstream signaling pathway activation. In contrast to the universal expression of IL-17RA, IL-17RE is mainly located on epithelial cells, keratinocytes or Th17 cells.^{25–27} As described above, IL-17RA is a shared receptor of the IL-17 family of cytokines. Thus, IL-17RE is believed to act as a specific functional receptor for IL-17C. IL-17C activates the NF-κB and MAPKs

pathways in both human colonic tumor cell lines and mouse intestinal epithelial cells.²⁵ Knockout or knockdown of the *Il17re* gene inhibits IL-17C-mediated NF- κ B and MAPKs activation in these cells.²⁵ *Il17re* deficiency also blocks the IL-17C-induced expression of inflammatory genes, antibacterial peptides and anti-apoptotic genes in IECs.²⁵ In agreement with these findings, gene silencing of the *Il17ra* gene abolishes IL-17C-induced NF- κ B and MAPKs activation.²⁵ Because Th17 cells express a high level of IL-17RE, these cells may also serve as target cells for IL-17C.²⁷ Indeed, *Il17re*-transgenic Th17 cells are hyper-responsive to IL-17C and produce elevated levels of IL-17 and IL-17F.²⁷ Similar to IL-17 signaling, the adaptor molecule Act1 is required for IL-17C-induced IL-17 and IL-17F production in Th17 cells. Our unpublished data from an ectopic expression system also show that Act1 interacts with IL-17RE. Thus, Act1 is most likely required for IL-17C signaling in other cells types that express high levels of IL-17RE, such as epithelial cells or keratinocytes.

IL-17D

Although IL-17D is most homologous to IL-17B, the signaling mediated by this orphan cytokine is barely understood. Early studies showed that IL-17D could stimulate IL-6, IL-8 and GM-CSF expression in endothelial cells or IL-6 and IL-8 expression in fibroblasts from chickens.⁹ Recent studies also showed that IL-17D increased human NK cell cytotoxic functions *in vitro* and induced MCP-1 production in tumor endothelial cells to recruit NK cells for tumor rejection *in vivo*.^{68,69} The receptor for IL-17D has not yet been identified.

THE BIOLOGICAL AND PATHOLOGICAL ROLES OF IL-17 FAMILY CYTOKINES IN THE MUCOSAL IMMUNE SYSTEM

IL-17 and IL-17F

IL-17 and IL-17F in infection. Both IL-17 and IL-17F are quickly released by innate immune cells (that is, ILC3) or adaptive Th17 cells.¹⁴ The released cytokines subsequently target epithelial cells or keratinocytes to induce the expression of inflammatory cytokines, chemokines and antibacterial peptides and protect the host from pathogenic infections.¹⁴ In contrast to the Th1-cell-mediated anti-intracellular bacterial responses, IL-17 and IL-17F typically generate anti-extracellular bacterial and antifungal responses. A deficiency in IL-17RA leads to decreased bacterial clearance and inflammatory gene production upon *Klebsiella pneumoniae* or *Staphylococcus aureus* infection in the lung.^{70,71} Consistently, *Il17a*- or *Il17f*-deficient mice show impaired defense responses against infection with extracellular pathogens such as *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Citrobacter rodentium*.^{72,73} Recently, an intestinal commensal bacterium [segmented filamentous bacteria (SFB)] was shown to induce intestinal Th17 development in the steady state by attaching to intestinal epithelial cells. Mice lacking SFB harboured fewer Th17 cells in the intestine and thus were susceptible to *Citrobacter rodentium* infection.⁷⁴ Moreover, the intestinal Th17 responses against *Citrobacter rodentium* required a physical interaction between

the intestinal epithelial cells and the microbes,⁷⁵ indicating that both the recognition of MAMP molecules and the location of the microbes are critical for the generation of proper adaptive immune responses.

Candida species are fungal species that frequently colonize the oral, intestinal, and vaginal surfaces and the skin of healthy individuals. These fungi help the host shape microbial communities in mucosal barriers and maintain immune system homeostasis. However, many *Candida* species are also opportunistic pathogens that cause fungal infections in the host. One oral opportunistic fungi (*Candida albicans*) strongly induces the differentiation of Th17 cells and neutrophil infiltration after infection.^{76,77} In the oropharyngeal candidiasis (OPC) model, *Il17ra*-, *Il17rc*- and *Il23p19*-deficient mice showed increased fungal burdens on their tongues, whereas *Il22*-deficient mice were only mildly susceptible to OPC infection; these results indicated that the IL-23-Th17-IL-17 axis was critical for the clearance of oral candidiasis.^{76,78} Mechanistically, IL-17 controls oral candidiasis infection via neutrophil recruitment and antimicrobial factor production, although one study has shown that the IL-17-mediated antifungal defense occurs independent of neutrophils.^{76,78} IL-17 signaling is also essential for the host defense against systemic infection with oral *Candida albicans*. A deficiency in IL-17 and IL-17RA but not IL-17F increased the susceptibility to systemic infection with this fungus.^{77,79} Recently, one study showed that NK progenitors lacking IL-17R signaling showed in the impairment of the development of functional NK cells in mice.⁸⁰ These mice were also defective in the production of NK cell-derived GM-CSF, which was critical for the antifungal activity of neutrophils.⁸⁰ In an *Aspergillus*-induced keratitis model, IL-17 signaling activated neutrophils for the antifungal response in an autocrine manner. A population of neutrophils constitutively expresses the transcription factor ROR γ t to produce IL-17 in response to IL-6 and IL-23.⁸¹ These neutrophils also respond to self-secreted IL-17 to produce reactive oxygen species (ROS) for fungal killing.⁸¹

In addition to extracellular bacteria and fungi, IL-17 also indirectly protects mice from intracellular bacterial infection. During *Francisella tularensis* infection, IL-17 may induce IL-12 production from myeloid cells to promote a Th1 response.⁸² Neutralization or genetic depletion of the *Il17a* gene increases bacterial dissemination in mice.⁸² Although it is not required for the clearance of *Mycobacterium tuberculosis* and *Mycobacterium bovis*, IL-17 promotes chemokine production to recruit IFN- γ -producing T cells against *Mycobacterium tuberculosis* infection in vaccine-induced immunity.^{83–85}

IL-17 and IL-17F in colitis and psoriasis. Inflammatory bowel disease (IBD) is an inflammatory disorder of the intestinal tract that is typically diagnosed as ulcerative colitis (UC) and Crohn's disease (CD). Clinically, the IL-17 level is elevated in both UC and CD patient specimens.^{86,87} IL-17F expression is higher in CD patients than UC patients.⁸⁸ Several genome-wide association studies (GWASs) have shown that the genes critical for Th17 responses and IL-17 signaling (that is, STAT3, IL-23R,

CCR6 and Act1) are associated with IBD pathogenesis in humans.^{89–92} Neutralization of IL-17 or IL-17 deficiency leads to enhanced dextran sodium sulfate (DSS)-induced colitis pathology in mice, indicating a protective role for IL-17 in this model.^{45,93} Conversely, another study showed that *Il17a*-deficient mice were resistant to DSS-induced colitis, suggesting a pathological role for IL-17.⁹⁴ This discordance is likely due to the variance in the intestinal microbiota in different facilities. During colitis, the growth factor FGF2 has been shown to synergize with IL-17 to induce the expression of genes involved in tissue repair and restore the damaged epithelium.⁹⁵ Deficiency in either FGF2 or IL-17 leads to impaired epithelial proliferation, uncontrolled Enterobacteriaceae outgrowth, and consequently worsened DSS-induced colitis pathology.⁹⁵ The dysregulated microbiota induces TGF β 1 expression in the model, which in turn triggers FGF2 expression in regulatory T cells.⁹⁵ Thus, during acute colitis Th17-derived IL-17 coordinates with Treg-derived FGF2 to repair intestinal epithelial damage. Both T-cell-derived FGF2 and IL-17 protected *Rag1*-deficient mice from a naive CD4⁺ T-cell transfer-induced colitis model.⁹⁵ However, IL-17F exacerbated the DSS-induced intestinal inflammation because *Il17f*-deficient mice were resistant to DSS challenge.⁴⁵

Psoriasis, which is a relapsing skin inflammatory disorder, is characterized by hyperplasia of the dermis. Both IL-17 and IL-17F are highly elevated in skin biopsies from psoriasis patients.^{19,96,97} Similar to IBD, GWAS data from psoriasis specimens show that IL-23R and Act1 are psoriasis-associated genes.^{98–100} In mice, intracutaneous injection of IL-23 causes psoriasis-like epidermal hyperplasia; this skin inflammation is ameliorated in *Il17a*-, *Il17ra*- or *Il22*-deficient mice.^{101,102} The TLR7/8 agonist imiquimod (IMQ) can also induce and exacerbate a psoriasis-like syndrome in mice. Studies have shown that *Il23p19*-, *Il17ra*-, and *Act1*-deficient mice are protected from IMQ-induced psoriasis compared with wild-type mice.^{103–105} K5.Stat3C transgenic mice in which Stat3 is constitutively activated in keratinocytes develop skin lesions similar to those of human psoriasis.¹⁰⁶ Either neutralization of IL-17 or deletion of the *Il17a* gene ameliorates 12-O-tetradecanoylphorbol-13-acetate-induced psoriasis in these mice.¹⁰⁶ In contrast to targeting IL-23 signaling, the inhibitory effects of targeting IL-17 signaling are less prominent in these animal models, indicating that alternative pathways may also contribute to the development of skin inflammation.^{103,104,106} On a cellular level, IL-17 synergizes with other cytokines, such as TNF α , IFN γ or IL-22, to induce the production of proinflammatory cytokines, chemokines and antimicrobial peptides from keratinocytes.^{107–109} Because the IL-23-Th17-IL-17 axis is critical for the pathogenesis of psoriasis, antibody targeting therapies that target IL-17 signaling (that is, brodalumab, ixekizumab and secukinumab) or IL-23 signaling (that is, ustekinumab, briakinumab, tildrakizumab and guselkumab) are being rapidly developed and have shown prominent outcomes in treating psoriatic diseases in different clinical trials.¹¹⁰

IL-17 and IL-17F in allergy. Clinical surveys demonstrate that both IL-17 and IL-17F levels are elevated in bronchial specimens from allergic asthma patients.^{111–113} Exogenous expression of both cytokines leads to increased infiltration of lymphocytes, neutrophils and macrophages, and mucus hyperplasia.^{45,67} Consistent with this finding, the transfer of ovalbumin (OVA)-specific Th17 cells into mice results in pulmonary inflammation and airway hyper-responsiveness (AHR) after OVA challenge.¹¹⁴ In an OVA-induced lung inflammation model, IL-17 promotes disease progression and IL-17F inhibits or has no effect on this allergic response.^{45,72,115} House dust mite-induced airway neutrophil infiltration also requires IL-17.¹¹⁶ However, another study showed that IL-23 but not IL-17 was essential for OVA-induced allergic rhinitis.¹¹⁷ In contrast to IL-17E, IL-17 contributes to pulmonary inflammation by promoting type 1 immunity related to neutrophilia rather than eosinophilia, which is mainly mediated by type 2 immunity. Indeed, IL-17 can induce the expression of chemoattractants such as CXCL1, CXCL2, CCL20 or β -defensin two in human airway epithelial cells to favour chronic inflammation in lung diseases.^{118–120} As discussed above, IL-17 may cooperate with other cytokines such as TNF α to amplify the expression of inflammatory genes that may contribute to the pathogenesis of chronic airway diseases. In addition to this effect, IL-17 also coordinates with innate PRR signaling pathways such as TLR signaling to synergistically induce proinflammatory gene expression in the human airway epithelium. Thus, cross-talk between IL-17 and TLR signaling may exacerbate viral respiratory infection-induced asthma or other chronic pulmonary diseases.^{121,122} Furthermore, IL-17 directly induces insensitivity of bronchial epithelial cells to steroids.¹²³ Recently, one study showed that IL-17 but not IL-17F directly drove pulmonary hyper-responsiveness by promoting smooth muscle contractions in the airway.¹²⁴ Because IL-17 also induces the production of mucins such as MUC5AC and MUC5B by airway epithelial cells,^{125,126} these findings indicate that IL-17 may promote pulmonary allergies by inducing airway remodelling in addition to its inflammatory effects.

IL-17 and IL-17F in cancer. IL-17 plays a protumorigenic role in different mouse tumor models, including those of the intestine, skin and lung. *Il17a* deficiency reduces intestinal tumorigenesis in both colitis-associated and spontaneous intestinal cancer mouse models.^{127,128} The loss of IL-23 signaling, which is critical for the generation of pathogenic Th17 responses, inhibits tumor growth in a spontaneous colon cancer mouse model; this finding is in agreement with the phenotype of *Il17a*-deficient mice.¹²⁹ As a consequence of the genetic lesions of colorectal cancer, either the early or late stage of colorectal tumors exhibit defects in their epithelial barrier integrity.¹²⁹ The barrier defect results in adenoma invasion by microorganisms and their products, which triggers IL-23-Th17-IL-17-induced protumorigenic inflammation.¹²⁹ Indeed, one such microorganism [the enterotoxigenic *Bacteroides fragilis* (ETBF)] induces pathogenic Th17 responses to promote

intestinal tumorigenesis in *Apc*^{Min/+} mice.¹³⁰ Recently, IL-17RA signaling in transformed enterocytes were demonstrated to be essential for intestinal tumor development,¹³¹ indicating that IL-17 directly promoted tumor cell proliferation; however, IL-17C signaling was also diminished in this system. IL-17 and IL-23 signaling also promote chemical-induced skin cancer development because a deficiency in IL-17, IL-17RA or IL-23 in mice inhibits the cutaneous carcinogenesis induced by 9,10-dimethyl-1,2-benzanthracene (DMBA) plus 12-O-tetradecanoyl-phorbol acetate (TPA).^{132–134} Neutralization of IL-17 in mice also ameliorates DMBA/TPA-induced skin cancer.¹³⁴ The role of IL-17 in lung cancer has been studied recently. *Il17a*-deficiency in Clara cell secretory protein (CCSP^{cre})/K-ras^{G12D} mice limits the lung tumor burden.¹³⁵ Similar to IL-17, IL-17F has been shown to promote intestinal tumor development in *Apc*^{Min/+} mice.¹³⁶ However, IL-17F had an opposing role during tumorigenesis in a colitis-associated colon cancer model.¹³⁷ Although its production is increased in the lung BALF of CCSP^{cre}/K-ras^{G12D} mice to a level similar to IL-17, IL-17F deficiency does not affect tumor formation in the lungs of these mice.¹³⁵

IL-17E and IL-17B

IL-17E and IL-17B in infection. Helminth infections are tightly linked to type 2 immunity of the host. IL-17E can strongly promote Th2 responses and thus has a pivotal protective role against helminths in the intestine. *Il17e*-deficient mice display lower efficiency in *Nippostrongylus brasiliensis* expulsion and reduced Th2 cytokine production.¹³⁸ Administration of IL-17E promotes Th2 cytokine production in c-Kit⁺FcεR1-NBNT cells and promotes worm expulsion.¹³⁸ In addition, IL-17E administration in RAG-deficient mice protects them from *Nippostrongylus brasiliensis* infection,¹³⁸ indicating that innate immune cells such as ILC2s rather than T or B cells maybe targeted by IL-17E for type 2 cytokine production. Another study showed that epithelial-derived IL-17E was critical for *Nippostrongylus brasiliensis* expulsion from the intestine.¹³⁹ Although many ILC2s (that is, MPP^{type2} cells, nuocytes and Ih2 cells) can promote type 2 immunity in response to IL-17E, the precise roles of IL-17E and these ILC2s in worm expulsion need to be determined in the future.⁹ Exogenous delivery of IL-17E also protects mice from *Trichuris muris* infection, whereas IL-17E deficiency in mice leads to impaired worm clearance.¹⁴⁰ Recently, one study showed that Act1 deficiency in epithelial cells resulted in a remarkable decrease in Lin[−]c-Kit⁺ cells and a delay in *Nippostrongylus brasiliensis* expulsion.⁵⁷ Adoptive transfer of Lin[−]c-Kit cells or combined injection of IL-25 and IL-33 rescued the phenotype in these mice.⁵⁷

The roles of IL-17B in infection are poorly understood. IL-17B is slightly induced in the intestine in response to *Citrobacter rodentium* infection.²⁵ Recently, IL-17B was demonstrated to protect mice from infection, whereas IL-17E exacerbated infectious pathogenesis in mice.⁶⁵

IL-17E and IL-17B in colitis. IL-17E expression is down-regulated in inflamed colons from IBD patients and DSS-treated mice.^{141,142} *In vivo* delivery of recombinant IL-17E inhibits the development of DSS-, 2,4,6-trinitrobenzenesulphonic acid (TNBS)-, or peptidoglycan (PGN)-induced acute colitis in mice.^{142–144} Mechanistically, the anti-colitic effect mediated by IL-17E is probably dependent on the activation of anti-inflammatory alternatively activated macrophages (AAMs) and the inhibition of CD4⁺ T-cell activation and their differentiation into inflammatory Th1/Th17 cells in the colon.^{141,142,144,145} Recombinant IL-17E even ameliorates oxazolone-induced type 2 colitis, indicating that IL-17E has a broad anti-inflammatory effect in the colon rather than selectively suppressing Th1/Th17 cytokine production.¹⁴⁴ A recent study showed that IL-17E was produced by intestinal epithelial cells during acute colitis and that mice deficient in IL-17E were protected from DSS-induced colitis.^{65,146} Furthermore, neutralizing IL-17E or IL-17RB with antibodies ameliorates the onset of oxazolone-induced colitis.¹⁴⁷ These contradictory results suggest that endogenous IL-17E signaling rather than the exogenous delivery of IL-17E might be pathogenic and contribute to intestinal inflammation. Although inflamed epithelial cells produce IL-17B, this cytokine demonstrates anti-inflammatory activity by antagonizing IL-17E-mediated intestinal inflammation. In contrast to *Il17e*-deficient mice, mice deficient in the *Il17b* gene exhibit aggravated colitis after DSS exposure.⁶⁵

IL-17E and IL-17B in allergies. Allergic responses depend to a large extent on the production of Th2 cytokines such as IL-4, IL-5 and IL-13 in mucosal barriers. Although it is critical for worm expulsion and anti-Th1/Th17 responses, IL-17E is a pathogenic factor during allergic diseases due to its induction of Th2 cytokines. The IL-17E level is higher in nasal lavages from allergic rhinitis patients than normal controls.¹⁴⁸ Upon allergen challenge, IL-17E is increased in the bronchial mucosa of asthmatic patients and the skin dermis of atopic subjects.¹⁴⁹ Consistently, IL-17E mRNA is increased in the airways of antigen-challenged mice.¹⁵⁰ Epithelial-specific transgenic IL-17E expression leads to enhanced mucus production and pulmonary inflammatory responses in mice, whereas neutralization of IL-17E with antibodies reduces type 2 inflammation and goblet cell hyperplasia in the allergic asthma animal model.^{151,152} *Il17e*-deficient mice also exhibit attenuated production of the Th2 and Th9 cytokines and reduced lung allergic inflammation.¹⁵³ Likewise, neutralization by soluble IL-17RB or genetic depletion of the *Il17rb* gene in mice ameliorates the pulmonary pathology induced by allergen challenge.^{150,154} IL-17E-induced mucous hypersecretion and AHR have been suggested to be primarily dependent on IL-13-STAT6 signaling.^{150,155} In addition to the induction of Th2 cytokines, one study showed that prolonged IL-17 expression in the lung induced NKT cell-dependent pulmonary arterial remodelling.¹⁵⁶ IL-17E also contributes to VEGF signaling-induced angiogenesis via the Erk/MAPK and PI3K/Akt pathways in asthma.¹⁵⁷ Moreover, blocking IL-17E in the airways of allergen-

challenged mice decreases the deposition of peribronchial collagen and the hyperplasia of airway smooth muscles.¹⁵⁸ IL-17E contributes to allergenic resources by orchestrating airway remodelling in addition to inducing airway type 2 inflammation. Thus, IL-17B shows opposing phenotypes to IL-17E during allergic asthma.⁶⁵

IL-17C

IL-17C in infection. Pathogens, such as *Citrobacter rodentium*, *Mycoplasma pneumoniae* and *Candida albicans*, and PAMPs from pathogens, such as the TLR5 agonist flagellin, can induce IL-17C expression in the intestine,^{25,159} lung,¹⁶⁰ kidney,¹⁶¹ and tongue.¹⁶² On a cellular level, several pathogens (that is, *Pseudomonas aeruginosa*, *Haemophilus influenza*, *Staphylococcus aureus*, *Citrobacter rodentium* and *Candida albicans*) trigger IL-17C production from bronchial epithelial cells,¹⁶³ keratinocytes,¹⁶⁴ intestinal epithelial cells,²⁵ and kidney epithelial cells.¹⁶¹ Several intestinal pathogens or opportunistic pathogens, such as *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Shigella flexneri*, *Enterobacter aerogenes* and *Proteus mirabilis*, can activate IL-17C transcription in intestinal epithelial cells.¹⁶⁵ On a molecular level, signals from the TLR and NOD2 pattern-recognition receptor mediate IL-17C induction in different types of epithelial cells.^{25,26,166} Both the TLR-Myd88-NF- κ B and TLR-TRIF-NF- κ B pathways are likely to be required for its induction.^{26,167,168} The production of IL-17C is also controlled by inflammatory cytokines (that is, TNF α and IL-1 β), which might be induced by PRR signaling during infection.²⁵ IL-17 and IL-17F also induce IL-17C expression in intestinal epithelial cells, albeit at a reduced level.²⁵ Because IL-17C targets Th17 cells to promote IL-17 and IL-17F production or indirectly induces the expression of the Th17 chemoattractant CCL20 in intestinal epithelial cells, the IL-17 family cytokines may cooperate with each other in a physiological or pathological manner at different mucosal surfaces. In addition to TLRs and inflammatory cytokine signaling, the transcription factor NF- κ B is likely to control the transcriptional activation of the *Il17c* gene.¹⁶⁹ TNF α also cooperates with IL-17 to amplify IL-17C expression in intestinal epithelial cells; this synergistic effect requires TNF α -induced NF- κ B, ERK and P38 expression and IL-17-induced AKT and C/EBP δ activation.¹⁷⁰

Similar to IL-17, IL-17C induces inflammatory gene and antimicrobial peptide expression either alone or in synergy with IL-22, indicating that IL-17C signaling maybe critical for the host defense response.²⁵ The kinetics of IL-17C induction during *Citrobacter rodentium* infection are similar to those of IL-22 in the colon.²⁵ Similar to IL-22, IL-17RE deficiency in mice results in an early mortality phenotype during infection.^{25,171} The induction of IL-17C occurs much earlier than IL-17, suggesting that IL-17C is an innate-like cytokine that functions during the early stage of infection. IL-17, which is produced later, coordinates with IL-17C and other cytokines for the comprehensive defense of infection at the epithelial edge.²⁵ The functional role of IL-17C signaling in antifungal immunity was also recently characterized. Although the IL-17C

mRNA is induced after oral *Candida albicans* infection, the body weight loss, fungal burden in infected tissues and skin lesions are similar between wild-type and *Il17c*- or *Il17re*-deficient mice with an oral, disseminated and cutaneous infection.^{76,162} The only noticeable phenotype is that mice lacking the *Il17c* gene show alleviated kidney tissue damage during systematic *Candida albicans* infection.¹⁶¹ Thus, in contrast to its protective role in the intestine, IL-17C signaling may cause mild tissue injury by promoting inflammation during fungal infections.

IL-17C in colitis and psoriasis. In addition to its protective role in the intestinal defense response, IL-17C signaling is also required for the maintenance of intestinal homeostasis during colitis. DSS-induced colitis causes the overgrowth and translocation of *E. coli* species into the basolateral side of the intestinal epithelium where they trigger IL-17C production from these cells via TLR signaling.^{26,165} Under colitis conditions, the monoclonization of *E. coli* in either germ-free mice or antibiotic-treated mice can sufficiently induce IL-17C expression in the colon.¹⁶⁵ IL-17C signaling maintains intestinal mucosal barrier integrity by inducing tight junction molecule or antibacterial gene expression in intestinal epithelial cells.^{26,172} The loss of IL-17C signaling in mice causes a severe body weight drop, enhanced intestinal epithelium lesions and less controlled inflammatory *E. coli* outgrowth in the colon.^{26,165,172}

Clinical studies from psoriasis patients show that IL-17C, IL-17 and IL-17F mRNA expression is significantly elevated in psoriatic skin.⁹⁶ IL-17C targets human primary epidermal keratinocytes to induce inflammatory gene and antibacterial peptide expression from these cells.^{19,26} IL-17C also synergistically cooperates with other inflammatory cytokines (that is, TNF α or IL-1 β) to amplify the expression of psoriasis-related genes in keratinocytes.^{19,26} In addition to keratinocytes, IL-17C triggers inflammatory gene production in human dermal microvascular endothelial cells.¹⁹ In contrast to the protective roles of IL-17C in colitis models, IL-17C signaling aggravates the pathogenesis of several psoriatic models in mice. The keratinocyte-specific overexpression of the *Il17c* gene in mice leads to the development of a spontaneous psoriasis-like phenotype of the skin with increased cutaneous angiogenesis and inflammation.¹⁹ Consistent with this finding, IL-17C mRNA expression is markedly increased in the skin lesions of an imiquimod-induced psoriasis mouse model.²⁶ Genetic depletion of either IL-17C or IL-17RE can efficiently protect mice from imiquimod-mediated skin inflammation and hyperplasia.²⁶

IL-17C in cancer. During the development of intestinal cancer, IL-17C is upregulated in both colitis-associated and spontaneous mouse intestinal tumor models.¹⁶⁵ Similar to IL-17, the expression of IL-17C is elevated in human colorectal cancers. Genetic depletion of the *Il17re* gene in mice greatly reduces intestinal tumor formation in both mouse intestinal tumor models.¹⁶⁵ Dysregulated Enterobacteriaceae (particularly *E. coli*) drives IL-17C upregulation primarily in IECs through

TLR-MyD88-dependent signaling during intestinal tumorigenesis. The translocated microbiota also strongly induces IL-17 expression in LP lymphocytes through both TLR- and inflammasome-induced signaling.¹⁶⁵ The dysregulated microbiota has been shown to drive IL-17 production in Th17 cells and to promote the growth of transformed enterocytes in colorectal cancer.¹³¹ However, microbiota-driven IL-17C primarily inhibits the apoptosis of transformed enterocytes by inducing Bcl-2 and Bcl-x_L expression in these cells in an autocrine manner to promote tumorigenesis.¹⁶⁵ Thus, IL-17C and IL-17 promote intestinal cancer development via distinct mechanisms, and the dysregulated microbiota, such as bacteria in the Enterobacteriaceae family, can mediate cancer pathogenesis by regulating both IL-17C and IL-17.

CONCLUSION

Recent progress in the field of mucosal immunity has revealed distinct roles for the IL-17 family of cytokines in different epithelial barrier surfaces. Although the epithelial cell-immune cell cross-talk mediated by the family members is critical for the coordination of immune responses against invading microorganisms, the dysregulation of this interaction often leads to inflammatory tissue lesions and even promotes tumorigenesis. Similar to IL-17, IL-17F is critical for host defense responses against bacterial and fungal infections. However, IL-17E has unique functions in anti-parasite and allergic responses and antagonizes Th17 responses during inflammation. Although it shares the same receptor set with IL-17E, IL-17B seems to antagonize IL-17E functions in colitis, extracellular bacterial infections and allergic asthma. The novel innate-like cytokine IL-17C coordinates with IL-17 to promote antibacterial responses and epithelial barrier integrity. Both dysregulated microbiota and chronic inflammation may over-activate the production of these two cytokines and promote intestinal cancer development or psoriasis pathogenesis. The *in vivo* function of IL-17D in the mucosa is unknown. The interplay of IL-17 family members with other cytokines to orchestrate different immune responses also requires further exploration. Anti-IL-17 therapy has been shown to have promising clinical outcomes for the treatment of inflammatory diseases including psoriasis. An improved understanding of the functional roles of IL-17 family cytokines in distinct epithelial barriers will benefit the diagnosis and therapy of inflammatory mucosal disorders in humans.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Natural Science Foundation of China (81430036, 81230075, 91429307, 31329002, 91329301 and 91542119), the 973 Program (2013CB944904), and the Science and Technology Commission of Shanghai Municipality (13JC1408900).

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