

Mechanisms controlling Th17 cytokine expression and host defense

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ABSTRACT

Th17 cells contribute to mucosal immunity by stimulating epithelial cells to induce antimicrobial peptides, granulopoiesis, neutrophil recruitment, and tissue repair. Recent studies have identified important roles for commensal microbiota and Ahr ligands in stabilizing Th17 gene expression in vivo, linking environmental cues to CD4 T cell polarization. Epigenetic changes that occur during the transition from naïve to effector Th17 cells increase the accessibility of *il17a*, *il17f*, and *il22* loci to transcription factors. In addition, Th17 cells maintain the potential for expressing T-bet, Foxp3, or GATA-binding protein-3, explaining their plastic nature under various cytokine microenvironments. Although CD4 T cells are major sources of IL-17 and IL-22, innate cell populations, including $\gamma\delta$ T cells, NK cells, and lymphoid tissue-inducer cells, are early sources of these cytokines during IL-23-driven responses. Epithelial cells and fibroblasts are important cellular targets for IL-17 in vivo; however, recent data suggest that macrophages and B cells are also stimulated directly by IL-17. Thus, Th17 cells interact with multiple populations to facilitate protection against intracellular and extracellular pathogens. *J. Leukoc. Biol.* 90: 263–270; 2011.

Introduction

CD4⁺ T cells are critical effector cells of adaptive immune responses. The differentiation of naïve to effector and memory T cells is complex with many checkpoints and balances along the way (reviewed in ref. [1]). In LNs, the presentation of exogenous Ag and costimulatory signals to naïve T cells primes their differentiation into specialized subsets. The route of Ag delivery or type of APC may influence T cell polarization. DCs are efficient at processing exogenous Ags into the MHC class II pathway and are surveyed by naïve T cells in LN subcortical

regions. Other APC populations include macrophages, B cells, basophils, and plasmacytoid DCs. The differentiation of naïve CD4 T cells into Th1 is important for controlling intracellular bacteria infections while Th2 cells initiate antibody responses against extracellular pathogens. Moreover, Th2 cells are critical for the expulsion of helminths. More recently, Th17 cells were found to be protective against infections at mucosal surfaces (reviewed in ref. [2]). Th17 cells work through multiple effector mechanisms, including coordinating granulopoiesis, neutrophil recruitment, induction of antimicrobial proteins and chemokines, germinal center formation, and antibody isotype switching [2–4]. The main effector cytokines associated with Th17 cells include IL-17A (IL-17), IL-17F, and IL-22 [5, 6], and they may express any combination of these. Although in vitro studies deciphered molecular mechanisms governing Th17 differentiation, the physiological circumstances under which this happens in vivo are still being elucidated, including the influence of endogenous and environmental factors. Understanding the maintenance and breadth of Th17 effector functions will reveal why they exist despite their potential for mediating autoimmune inflammation. Non-CD4⁺ T cell populations such as $\gamma\delta$ T cells and NK cells are also capable of producing Th17 cytokines, suggesting that Ag-independent triggers can be responsible for initiating this type of inflammation commonly associated with Th17 immunity.

Th17 DIFFERENTIATION

Differentiation of T cell subsets is coordinated by lineage-specific transcription factors [1]. The anti-inflammatory cytokine TGF- β drives Treg differentiation by inducing Foxp3 [7]. IL-6 prevents the induction of Foxp3 by TGF- β and instead directs T cells toward the Th17 lineage by inducing *rorc* and *rora*, encoding ROR γ t and ROR α , respectively [8–10]. This mechanism by which IL-6 promotes Th17 differentiation involves STAT3 activation [11, 12] and the production of IL-21 by T cells [13–16]. On the other hand, TGF- β indirectly supports Th17 polarization by inhibiting Th1 and Th2 differentiation [17, 18]. The acquisition of inflammatory potential in Th17

Abbreviations: Ahr=aryl hydrocarbon receptor, CD40/62L=CD40/62 ligand, EAE=experimental autoimmune encephalomyelitis, FICZ=6-formylindolo[3,2-b]carbazole, Foxp3=forkhead box p3, HCO₃⁻=bicarbonate, iNKT cell=invariant NK T cell, LTi cell=lymphoid tissue inducer cell, PIGR=polymeric immunoglobulin receptor, RBP-J=recombination signal-binding protein-J, Reg3 β/γ =regenerating islet-derived family β/γ , ROR=retinoid-related orphan receptor, SCF=stem cell factor, SFB=segmented filamentous bacteria, T-bet=T-box expressed in T cells, TCDD=2,3,7,8 tetrachlorodibenzodioxin, Treg=regulatory T cell

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cells is driven by IL-23: culturing Th17 cells with IL-23 results in inflammatory cytokine production and the ability to transfer disease, whereas culturing Th17 cells with TGF- β plus IL-6 causes them to produce IL-10 [19, 20]. This effect may be explained by the ability of IL-23 to induce T-bet expression in Th17 cells [19, 21]. Ghoreschi et al. [19] compared transcriptional profiles of conventional Th17 cells generated with IL-6 plus TGF- β [Th17(β)] versus Th17 cells generated with IL-6 plus IL-23 [Th17(23)] and found that over 2000 genes were differentially expressed. For instance, Th17(23) cells expressed higher levels of *Tbx21*, *Il18r1*, *Cxcr3*, and *Il33*, whereas Th17(β) cells expressed higher levels of *Il9*, *Il10*, and *Ccl20*. IL-23 can also directly promote Th17 differentiation by increasing *rorc* expression in combination with IL-1 β and IL-6 [19]. Overall, these data suggests that distinct subsets, Th17(β) versus Th17(23), can be identified by their transcriptional profile, and these populations differ in their ability to mediate disease. The positive impact of IL-1 β on Th17 differentiation suggests that the multitude of endogenous and exogenous factors, which stimulate inflammasome activity, can support Th17-mediated inflammation [22–24].

STAT3 coordinates Th17 differentiation by binding to promoters for many Th17 genes including *rorc*, *rore*, *il17a*, *il17f*, *il6ra*, *il21*, and *il23r* [25]. Humans with STAT3 deficiency have impaired Th17 responses [26–29], and the induction of experimental autoimmune diseases requires STAT3 signaling in CD4 T cells [11, 30], suggesting that this molecule could be a useful therapeutic target. Cytokines that can prime Th17 differentiation through STAT3 include IL-6, IL-9, and IL-21 [11, 12, 15, 31]. IL-27 is similar to IL-6 in that it signals through gp130 and STAT3 [32–34]; however, IL-27 inhibits Th17 differentiation, suggesting that STAT3 activation in itself is not sufficient or that STAT1, which is also activated by IL-27, has a dominant inhibitory effect on Th17 differentiation [35–37]. Aside from Th17 differentiation, STAT3 has other functions, including supporting Th2 differentiation, Treg function, and peripheral T cell proliferation and survival [25, 38, 39]. STAT3 has also been linked to IL-17 production by CD8 T cells [40, 41]. In contrast, some naturally arising Th17 cells in the thymus are STAT3-independent [42]. Altogether, this suggests that STAT3 signaling may be specifically required for the acquisition of IL-17 potential in secondary lymphoid tissues.

SFB INDUCE LOCAL AND SYSTEMIC Th17 RESPONSES

The intestinal microbiota influences various aspects of immunity, including the maturation of gut-associated lymphoid tissue, IgA class switching, and the recruitment of activated lymphocytes (reviewed in ref. [43]). As microbial products can have pro- or anti-inflammatory effects, they influence the basal level of inflammation in the gut. One mechanism by which this occurs involves TLR stimulation on DCs, resulting in their migration to mesenteric LN, where they activate T cells. The T cells may respond by driving IgA class switching in B cells or the expression of antimicrobial defensins from intestinal epithelial cells [43]. Microbiota can also impact systemic immune responses, including susceptibility to autoimmunity or allergy,

and understanding their role in shaping inflammation has therapeutic applications.

Commensal bacteria support steady-state Th17 levels, as germ-free mice lack Th17 cells in the intestinal lamina propria [44–47]. The presence of SFB in the gut was recently found to be an important contributor to Th17 polarization [48, 49]. The emergence of Th17 cells correlates well with SFB colonization around weaning time [46, 50], and colonization of mice with SFB significantly increases IL-17 levels [48, 49]. SFB are transmitted through the fecal-oral route, inhabit a number of vertebrate species, and localize to small intestinal epithelial cells [50–52]. In addition, SFB are found in rainbow trout [53]. As SFB adhere to Peyer's patches and stimulate IgA responses in the gut and serum [48, 54, 55], they could assist in preventing bacterial translocation across the epithelium. Host PRRs that drive Th17 differentiation in response to SFB have not been elucidated, although serum amyloid A contributes to the effect [49]. It is notable that MyD88^{−/−} × Toll/IL-1R domain-containing adaptor-inducing IFN- β ^{−/−} mice have normal Th17 numbers in lamina propria [44], suggesting that TLR signals do not impact steady-state levels of Th17 cells. SFB colonization in the gut was found to enhance autoimmune arthritis and EAE [56, 57], demonstrating its impact on systemic Th17 responses. In addition to increasing IL-17 levels, SFB increases IFN- γ and IL-4 production in lamina propria, suggesting a positive impact on Th1 and Th2 differentiation as well [48]. In contrast, the abundance of Tregs found in colonic mucosa is maintained in part by Clostridium species [58]. Thus, microbial species differentially influence the intestinal Th cell balance, impacting systemic adaptive immunity.

THE Ahr SUPPORTS Th17 POLARIZATION AND IL-22 PRODUCTION

The Ahr is a cytosolic sensor for a broad range of chemicals containing two carbon ring systems, including tryptophan derivatives (reviewed in ref. [59]). Among the most studied Ahr agonists are TCDD and FICZ, a tryptophan-derived photoproduct. Ligation of Ahr results in its nuclear translocation and binding to gene promoters containing dioxin-responsive elements [59]. Tissues that contact the external environment express high levels of Ahr, such as the intestine, lung, and liver. Among the numerous processes regulated by Ahr are neurogenesis, vascularization, circadian rhythm, liver development, metabolism, and cell stress [59]. In addition, the role of Ahr expression by individual cell populations such as hematopoietic stem cells is actively being studied (reviewed in ref. [60]).

The finding that Ahr-deficient mice have fewer Tregs and enhanced susceptibility to autoimmunity supports its role as an immunosuppressive molecule [61, 62]. TCDD and the endogenous ligand 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester were found to induce Foxp3 and functional Tregs [63–66]. On the other hand, FICZ preferentially supports Th17 differentiation [62, 67], suggesting that the binding affinity for Ahr differentially impacts gene expression. This could be a result of higher expression levels of Ahr in Th17 cells compared with Tregs [68, 69], resulting in increased sensitivity to Ahr ligands. Alternatively, the kinetics of Ahr activa-

tion may be responsible for functional differences between these ligands, as FICZ but not TCDD is degraded by xenobiotic metabolizing enzymes [59]. The expression of Ahr by phenotypically naïve CD62L⁺ cells [68] suggests a possible feedback loop in which the presence of Ahr ligands during Th polarization helps to maintain Ahr expression in effector/memory T cells. Ahr does not affect the expression of *rorc* or *rora* in developing Th17 cells but rather supports Th17 differentiation by directly inhibiting STAT1 and STAT5 [67, 68]. Ahr deficiency also impairs IL-22 responses [69], suggesting the involvement of endogenous ligands. The Notch pathway may provide a physiological target to regulate inflammation, as RBP-J stimulation increases IL-22 production through Ahr [70]. Notably, RBP-J-deficient mice were sensitive to Con A-induced hepatitis as a result of a lack of IL-22, and Notch signaling increased an endogenous Ahr agonist in Th17 cells. In human T cells, Ahr specifically enhances IL-22 production without affecting IL-17 [71, 72]. In addition to CD4 T cells, Ahr promotes IL-22 production by $\gamma\delta$ T cells [73], and human immature NK cells required IL-1 β to maintain Ahr expression and IL-22 potential [74]. Thus, Ahr expression in multiple lymphocyte subsets contributes to their IL-22 potential, and Ahr ligands have distinct effects on T cell differentiation.

Th17 STABILITY, PLASTICITY, AND EPIGENETICS

Many studies have focused on the differentiation of naïve CD4⁺ T cells into effector subsets; however, recently, there has been attention toward understanding the interconversion among subsets. The balance between Tregs and Th17 cells in culture is controlled by various factors including IL-6, IL-1, IL-23, and retinoic

acid [8, 75–77]. Moreover, some CD4 T cells at mucosal sites co-express Foxp3 and ROR γ t [78, 79], suggesting the local milieu determines whether Tregs or Th17 cells are preferentially induced in vivo. DCs play an important role in T cell polarization, and DCs activated via dectin-1 but not TLR9 are able to stimulate IL-17 production from Foxp3⁺ ROR γ t⁺ cells [76]. This population that coexpresses Foxp3, ROR γ t, and IL-17 functions as suppressors in human and mouse models [80, 81]. Th17 cells are also capable of converting into Th1 or Th2 lineages but not vice versa (Fig. 1 and refs. [82, 83]). For instance, the presence of IFN- γ and/or IL-12 will cause Th17 cells to up-regulate T-bet and produce IFN- γ [84, 85]. It has been suggested that IL-17⁺ IFN- γ ⁺ cells are derived from Th17 and can be identified by the surface marker CD161 [86]. Simply transferring Th17 cells into lymphopenic hosts will also result in their Th1 conversion [83, 87]. CD8 T cells producing IL-17 can switch to IFN- γ production in vivo [41], suggesting a fundamental mechanism underlying effector plasticity in CD4 and CD8 lineages.

The expression of Th17 effector cytokines is associated with epigenetic changes in promoter regions. The combination of TGF- β and IL-6 causes histone acetylation at the *il17a* and *il17f* promoters, enhancing the accessibility of chromatin to transcription factors [88]. STAT3, which is activated through IL-6, promotes epigenetic modifications associated with the Th17 signature [25]. The conversion of human Tregs to Th17 by allogeneic stimulation required histone deacetylation [89]. Histone trimethylation maps revealed that *Tbx21*, encoding the Th1 transcription factor T-bet, has a broad spectrum of epigenetic states, explaining how multiple Th subsets can be conditioned for IFN- γ production [90]. This mechanism may underlie the basis for Th plasticity. Mapping DNase I hypersensitivity sites revealed that Th17 cell activation in the presence of IL-12 modifies the IFN- γ promoter,

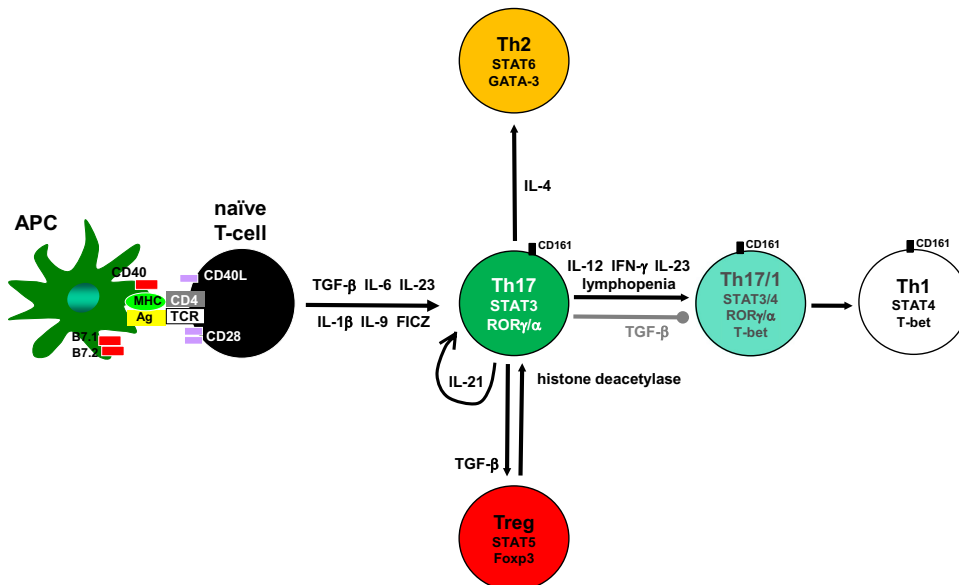


Figure 1. Extracellular factors controlling Th17 plasticity. CD4 T cell effector differentiation requires antigen and co-stimulatory signals derived from APCs. The presence of TGF- β and IL-6 induces IL-21 in T cells, which acts in an auto-crine manner through the transcription factor STAT3 to establish Th17 commitment. IL-23 and IL-9 also activate STAT3 to promote Th17 differentiation. The tryptophan photoproduct FICZ induces IL-17 through the Ahr. The transcription factors ROR γ and ROR α function to stabilize IL-17 expression. Removing TGF- β from the milieu results in Th17 cells converting to Th1, preceded by an intermediate ROR γ ⁺/ α ⁺ T-bet⁺ CD161⁺ stage. IL-23 also up-regulates the expression of T-bet and IFN- γ in Th17 cells. Other signals resulting in Th1 conversion include IL-12, IFN- γ , and lymphopenia. In addition, Th17 cells are capable of converting into Tregs and vice versa. For instance,

histone deacetylase activity promotes Treg conversion into Th17, suggesting that an epigenetic mechanism contributes to their reciprocal relationship. Further, stimulating Th17 cells with IL-4 increases GATA-binding protein-3 (GATA-3) expression and Th2 conversion. Therefore, effector Th17 cells are highly adaptable to their cytokine microenvironment, which may partially explain their association with pro- and anti-inflammatory functions.

and accessibility to the *il17a* locus was limited to Th17 cells [91]. Thus, studying the epigenetic state of histones at promoters associated with Th lineages has contributed to our understanding of T cell differentiation and stability.

INNATE SOURCES OF IL-17 AND IL-22

Although CD4⁺ T cells are major sources of IL-17 and IL-22 [92], some innate cell populations can also produce Th17-type cytokines when stimulated with IL-23 (Table 1). $\gamma\delta$ T cells are prominent sources of IL-17 in a number of models (reviewed in ref. [101]), including EAE, where IL-17 can be independent of TCR stimulation [109]. iNKT cells produce IL-17 and IL-22 in response to heat-killed bacteria [108]. In lymphocyte-deficient mice, the IL-23/IL-17 axis contributes to inflammatory bowel diseases [96, 110]. In this case, Gr-1⁺ CD11b⁺ cells were a significant source of intestinal IL-17 [96]. Neutrophil-derived IL-17 was also reported in LPS-induced lung inflammation [97], kidney ischemia-reperfusion injury [98], and systemic vasculitis [99]. TLR2 stimulation induced IL-17 in macrophages [100]. Subsets of mucosal NK cells have been found to produce IL-22 [94, 105, 106]. LT α -like cells identified as CD4⁺ CD3⁻ are an early source of IL-17 and IL-22 following treatment with zymosan or flagellin [102, 103]. These cells require the common γ chain for development and express IL-23R, Ahr, and ROR γ t. DCs were upstream of the LT α cell response, possibly as a result of their specialized role in amplifying IL-6 levels following treatment with PAMPs [102]. In response to *Citrobacter rodentium* infection, LT α cells were critical for the IL-22 production and host defense [104]. Further, reconstituting ROR γ ^{-/-} mice with LT α cells restored IgA levels through the induction of isolated lymphoid follicles, independently of T cells [111]. Another innate population identified as Thy1⁺ lineage⁻ CD4⁻ Sca-1⁺ CCR6⁺ was critical for bacteria-driven innate colitis [107]. This population expresses ROR γ t and mediates colitis through IL-17. Altogether, multiple innate cell types produce IL-17 and/or IL-22 in a ROR γ -dependent manner following IL-23 treatment. Studying their physiological roles can help us to understand why T cells evolved to become specific and specialized IL-17 producers. Further, this information identifies pathways that can be used to trigger Th17 effector cytokines in lymphopenic patients.

POTENTIAL EFFECTOR MECHANISMS OF TH17 CYTOKINES IN THE MUCOSA

One of the earliest functions described for IL-17 was its ability to stimulate granulopoiesis in vivo [112]. This is not a direct effect

of IL-17 on hematopoietic progenitors but rather, is mediated by the induction of G-CSF and SCF in epithelial cells (Fig. 2 and refs. [93, 113]). IL-17 also contributes to hematopoietic recovery following γ radiation [114]. The action of IL-17 on bronchial epithelial cells causes them to produce IL-8 and MIP-2, resulting in neutrophil recruitment to the lung [115, 116]. In addition, IL-17 mediates neutrophil recruitment to the peritoneum through keratinocyte-derived chemokine [117]. Other important functions of IL-17 on lung epithelium include the induction of antimicrobial genes (β -defensins, S100 family) and HCO₃⁻ secretion through cystic fibrosis transmembrane conductance regulator [2, 118]. Interestingly, carbonate ion increases bacterial membrane permeability and susceptibility to human β -defensin 2 [119]; thus, the coinduction of defensin gene expression and HCO₃⁻ transport may be an important mechanism by which IL-17 mediates mucosal immunity (Fig. 2). The variety of genes induced by IL-17 on epithelial cells impacts host resistance to many bacterial and fungal pathogens (reviewed in ref. [120]).

Although antibody responses were found to be diminished in IL-17^{-/-} and IL-23p19^{-/-} mice [121, 122], it was unclear if this was a result of the direct action of IL-17 on B cells. Recent studies have found that IL-17 directly promotes B cell isotype switching and germinal center formation [3, 4, 123, 124]. This is relevant to autoimmunity, as systemic lupus erythematosus patients have high serum levels of IL-17, which sustained peripheral B cell survival, proliferation, and IgM secretion [124]. Th17 cells also mediated B cell recruitment to the lung and expression of the PIGR on airway epithelium [125]. Thus, Th17 cells promote multiple aspects of humoral immunity (Fig. 2).

The degree to which different Th17 cytokines have redundant functions in mucosal immunity is also being explored. Although IL-17RA is required for host defense, multiple IL-17 family members signal through IL-17RA (IL-17, IL-17F, IL-25; reviewed in ref. [126]). Mice that are double-deficient for IL-17 and IL-17F, but not single-deficient mice, are susceptible to systemic *Staphylococcus aureus* infection, indicating partially redundant roles for these cytokines [127]. On the other hand, expression of both IL-17 and IL-17F was required for the induction of β -defensins and immunity to oral *C. rodentium* infection. In conjunction with IL-17, IL-22 increases the expression of G-CSF and antimicrobial genes including lipocalin-2 in lung epithelium [128]. Further, IL-22 enhances the clonogenic potential of lung epithelium independently of IL-17 and tissue repair following injury. As a result, IL-22 is required for host defense and survival following pulmonary *Klebsiella pneumoniae* infection [128]. In the gut, IL-22 has similar functions and mediates protection to *C. rodentium* through the induction of antimicrobial genes (Reg3 β and Reg3 γ) and

TABLE 1. Cellular Sources of IL-17 and IL-22

Lymphocytes	IL-17 refs.	IL-22 refs.	Nonlymphocytes	IL-17 refs.	IL-22 refs.
CD4 ⁺ T cells	92, 93	94, 95	Neutrophils (Gr-1 ⁺ CD11b ⁺)	96–99	
CD8 ⁺ T cells	40, 41		Macrophages	100	
$\gamma\delta$ T cells	reviewed in 101	reviewed in 101	LT α -like (CD4 ⁺ CD127 ⁺ CD3 ⁻)	102, 103	102–104
NK cells		105, 106	Innate lymphoid cells (Thy1 ⁺ lin ⁻ CD4 ⁻ Sca-1 ⁺ CCR6 ⁺)	107	
iNKT cells	108	108			

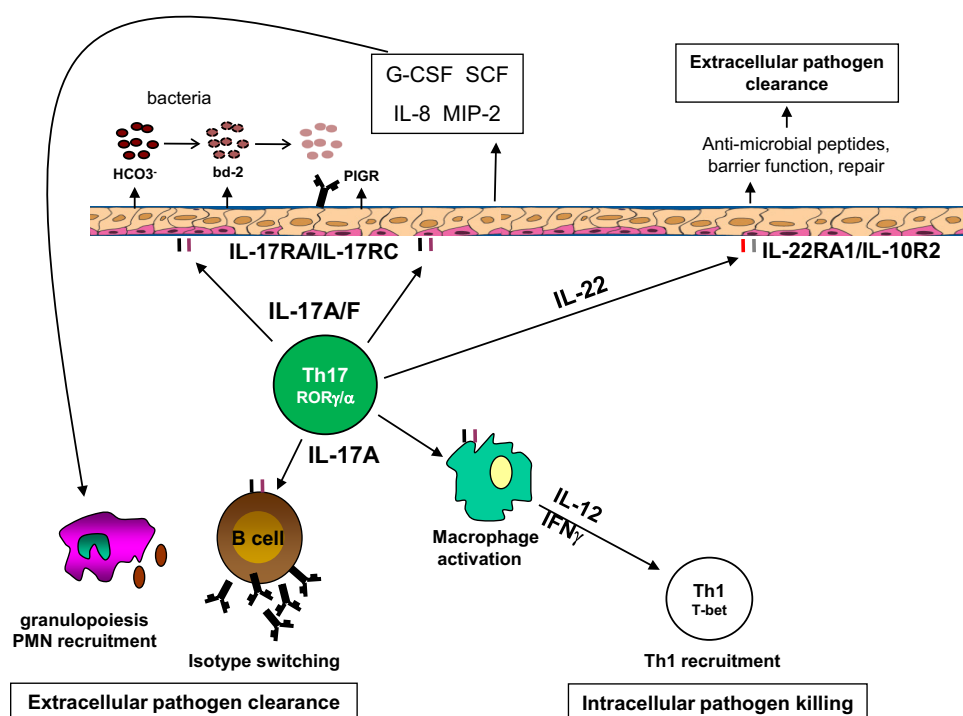


Figure 2. Th17 effector functions in the lung. IL-17 and the related cytokine IL-17F stimulate lung epithelial cells through the IL-17RA/IL-17RC complex, inducing mediators that promote granulopoiesis and neutrophil recruitment to the site of infection (G-CSF, SCF, IL-8, MIP-2). In addition, IL-17 facilitates HCO_3^- secretion and expression of anti-microbial peptides [i.e., β -defensin-2; (bd-2)], which directly promote bacterial membrane lysis. IL-22 stimulates the IL-22RA1/IL-10R2 complex on lung epithelium, facilitating injury repair and antimicrobial gene expression. In addition to these functions, IL-17 directly stimulates macrophages to produce IL-12, enhancing Th1 immunity to intracellular infections. IL-17 promotes humoral immunity by directly stimulating B cells to undergo isotype switching as well as increasing expression of the PIGR on lung epithelium. In this manner, Th17 cells support memory responses to extracellular pathogens.

maintenance of colonic epithelial integrity [129]. In toxoplasmosis, however, IL-22 was found to be proinflammatory [130]. Other important targets of IL-22 in vivo include keratinocytes, liver, and pancreas (reviewed in ref. [95]). Overall, Th17 cells produce multiple effector cytokines with partially overlapping roles in immunity.

CONCLUDING REMARKS

Environmental factors controlling Th17 responses in vivo are actively being investigated. Maintaining a reservoir of Th17 cells in the gut is important for barrier functions and preventing *Salmonella typhimurium* dissemination [131]. However, the impact of the intestinal microenvironment, including the presence of SFB, on systemic Th17 responses remains an interesting question. The plastic nature of Th17 cells underlies the importance of controlling its expression and localization, and whether Th17 responses are intrinsically or extrinsically regulated in vivo is unclear. The longevity of Th17 cells following intranasal infection was of shorter duration than the Th1 pool generated with systemic infection [132], and this was associated with decreased expression of the survival molecule Bcl-2 in $\text{CD}27^-$ IL-17 $^+$ T cells compared with $\text{CD}27^+$ IFN- γ^+ T cells. Although innate immune cells are capable of producing IL-17 and IL-22, the selective advantage for CD4 T cells to acquire this potential suggests that IL-17 is very important for secondary immune responses. In support, IL-17 contributes to vaccine-induced immunity by increasing Th1 cell recruitment to the site of infection (Fig. 2 and ref. [133]). Although IL-17 effector functions were initially studied on epithelial cells, leukocytes are also important targets for IL-17 in vivo. For instance, IL-17 conditions macrophages for IL-12 production and promotes Th1 immunity to the intracellular pathogen *Francisella*

tularensis [134]. Overall, selectively targeting the IL-17 pathway on cell populations may be a way to promote immunity while minimizing unwanted side-effects such as autoimmune inflammation.

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KEY WORDS:

IL-17 • IL-22 • STAT3 • segmented filamentous bacteria • aryl hydrocarbon receptor