CD4+ T-cell subsets and host defense in the lung

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Summary

CD4+ T-helper subsets are lineages of T cells that have effector function in the lung and control critical aspects of lung immunity. Depletion of these cells experimentally or by drugs or human immunodeficiency virus (HIV) infection in humans leads to the development of opportunistic infections as well as increased rates of bacteremia with certain bacterial pneumonias. Recently, it has been proposed that CD4+ T-cell subsets may also be excellent targets for mucosal vaccination to prevent pulmonary infections in susceptible hosts. Here we review recent findings that increase our understanding of T-cell subsets and their effector cytokines in the context of pulmonary infection.

Keywords

Introduction

CD4+ T-helper (Th) cells are critical components of the adaptive immunity in the lung (Fig. 1). The development of these cells arises after priming with antigen presented by class II major histocompatibility complexes (termed signal 1). Further activation occurs after the engagement of costimulatory molecules and their receptors expressed on both antigen-presenting cells (APCs) and T cells (termed signal 2). This second signal is critical for both generating antigen-specific effector T cells as well as memory cells. Presentation of antigen in the absences of costimulation can result in T-cell anergy. Final effector function is due to cytokine/growth factor-directed CD4+ T-cell differentiation (signal 3). This latter aspect of differentiation is driven by lineage-specific transcription factors as well as changes in chromatin remodeling. The critical role of CD4+ T cells in lung immunity and pulmonary host defenses was clearly demonstrated by the high incidence of pulmonary infections as a complication of human immunodeficiency virus (HIV) infections/acquired immunodeficiency syndrome (AIDS) (1–3).

CD4+ T-helper subsets

Th2 cells

Th2 CD4+ T-cells differentiate from naive precursors under the direction of the transcription factor GATA3 and signal transducer and activator of transcription 6 (STAT6) (4). Effector cytokines produced by Th2 cells include interleukin-4 (IL-4), IL-5, and IL-13. GATA3 binds directly to the *Il4* locus, and IL-4 and signaling via STAT6 is critical for further Th2 proliferation and lineage commitment (4). Th2 effector cytokines mediate immunity against

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infections with helminths (Fig. 2). Deletion of *Gata3* in mice results is embryonic lethal but conditional deletion of *Gata3* in T cells confirms the essential role of this transcription factor in Th2 differentiation and the expulsion of helminths from the gastrointestinal tract (5). IL-5 is an essential growth factor for eosinophilopoiesis (6, 7). Mice with homozygous deletion of *Il5* have substantial reduction in both peripheral and bone marrow eosinophils (6, 7). In contrast, overexpression of IL-5 protein results in substantial eosinophilia in blood and tissues (8). IL-13 signals through a receptor complex of IL13RA1 and IL4Rα and activates STAT6 signaling. These receptors are expressed on airway epithelium as well as airway smooth muscle. In bronchial epithelium, IL-13 is a major factor in mucous production and goblet cell differentiation in the airway (9, 10). Moreover, IL-13 signaling via STAT6 in airway smooth muscle and in airway epithelium leads to airways hyperresponsiveness to methacholine (9, 10). These cells and effector cytokines have been implicated in diseases such as allergic rhinitis, atopic dermatitis, and asthma (11). Anti-IL-5 has been investigated in asthma and although initial studies did not show clear cut efficacy (12), but subgroups of patients with high sputum eosinophilia respond to IL-5 blockade (12). Similarly, initial studies with IL-13 blockade were also negative, but recently, studies suggest that by stratifying patients with IL-13 driven asthma (by assessing the serum level of periostin, an IL-13 regulated gene in lung epithelium) can identify subgroups who respond to anti-IL-13 (13). In addition to asthma, IL-13 has been implicated in fibrotic processes in the lung in response to drugs such as bleomycin (14–16).

Th2 cells also facilitate B-cell differentiation and antibody responses to T-cell-dependent protein antigens (17), including the development of an anti-immunoglobulin E (IgE) response. It has been recently recognized that Th2 cell differentiation is not only regulated by IL-4 but also several cytokines produced by the lung epithelium including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 (17). It has been shown recently that polymorphism in both IL-33 and it receptors ST2 are associated with asthma, strongly implicating Th2 cells and specifically the IL-33 ST2 signaling pathway in this disease.

Th1 cells

Th1 cells, initially described by Mossman and Coffman (18), were defined by their ability to express interferon-γ (IFN-γ). Differentiation of CD4$^+$ Th1 cells is controlled by the transcription factors T-bet (19) and STAT4. Differentiation is controlled by IL-12p70, which is a heterodimer of IL-12p35 and IL-12p40 subunits (20). However, both *in vitro* and *in vivo* Th1 differentiation can be independent of IL-12. One critical IL-12 independent pathway is through the induction of type I interferons that can facilitate Th1 differentiation in certain situations (21). IFN-γ which signals via a receptor complex consisting of two IFN-γR1 and two IFN-γR2 chains can signal in a autocrine paracrine fashion to further amplify Th1 differentiation and lineage commitment. IFN-γ receptors are expressed on a wide variety of cells including myeloid cells including macrophages and dendritic cells (DCs) as well as structural cells in the lung such as epithelial cells and fibroblasts (22). IFN-γR1 and IFN-γR2 activate Janus-associated kinases 1 and 2 (JAK1/2), which phosphorylates STAT1. STAT1 undergoes homodimerization and translocation to the nucleus and binds to DNA-encoded γ-activated sequences (GAS) that ultimately control gene transcription (22).

IFN-γ is critical for mediating immunity and host resistance to many intracellular infections including *Mycobacterium tuberculosis*, *Listeria moncoytogenes*, and *Salmonella typhimurium*. Patients with mutations IL-12p40, IFN-γ, or receptors for IL-12 or IFN-γ have increased susceptibility to intracellular infections due to these organisms (23, 24). Patients with IFN-γ receptor mutations can develop disseminated infection with bacillus Calmette-Guerin (BCG) that is resistant to antibiotics and IFN-γ therapy (23, 25). Patients with IL-12p40 mutations can also develop BCG or *S. typhimurium* infection but

theoretically can respond to IFN-γ (24). Thus, there is strong evidence that this pathway is essential for human control of these intracellular pathogens.

Th17 cells

Th17 cells are recently described effector lineage of T-helper cells that produces IL-17A, IL-17F, IL-21, IL-22, and IL-26 (the latter expressed in human cells). Th17 cells differentiate under control of the transcription factors retinoid orphan receptor-γ (RORγ), ROR-α, and STAT3 (26, 27). It was initially believed that one of the critical instructional cytokines for Th17 differentiation was IL-23 (28); however, IL-23 receptors are not expressed on naive CD4+ T cells. Landmark studies published in 2005 showed that these cells develop independently of STAT4 or STAT6 as well as Tbet or GATA3 (29, 30). These data implicated that Th17 cells were a distinct CD4+ T-cell lineage (29, 30). Th17 differentiation can occur with stimulation with transforming growth factor-β (TGF-β) and IL-6 (31–33). Moreover this cytokine/growth factor combination induces the expression of IL-23R (31–33). Signaling via IL-23 allows terminal differentiation and expansion of Th17 cells (34). Another critical effector cytokine produced by Th17 cells is IL-22, which is controlled by IL-23 as well as the transcription factor the arylhydrocarbon receptor (Ahr) (35). IL-21 (36, 37) can function in an autocrine manner to further expand Th17 differentiation (Fig. 1). It has been recently been shown *in vivo* that TGFβ activation and thus differentiation of Th17 cells requires activation of latent TGFβ by αv inetgrins (38, 39). This pathway is not required for IL-17 production by γδ T cells (38, 39).

T-follicular helper cells

T-follicular helpher (Tfh) cells are a sub-group of CD4+ T cells that are located in the B-cell follicle region of secondary lymphoid tissues including lymph nodes and bronchial associated lymphoid tissues in the lung. These cells regulate T-cell-dependent B-cell activation through the expression of CD40L and IL-21 (40). These cells develop under the control of the transcription factor Bcl-6 (40) and are also regulated by inducible costimulatory (ICOS).

T-regulatory cells

Treg differentiation is controlled by the transcription factors Foxp3 and STAT5 (41). These cells are essential for mediating tolerance to inhaled antigen in the lung (41). Deletion of these cells or abrogating their effector molecules, which include IL-10 and TGFβ, prevent airways sensitization to allergen as well as allergic inflammation (41). These cells can suppress the effector activity of many T-helper subsets and can be thymically derived (natural Tregs) or induced in the periphery (iTregs). An exhaustive review of these cells is beyond the scope of this chapter, but the reader is referred to excellent thorough reviews (41, 42) of these cells if they seek a more in depth description of these cells.

Non-CD4+ T-helper cell sources of Th1/Th2/Th17 effector cytokines in the lung

Other cells in the lung exist that produce many of the same effector cytokines as Th1, Th2, or Th17 cells including innate lymphoid cells, natural killer (NK) cells, and γδ T cells. γδ T cells are resident in mucosal sites including the lung and can produce IFN-γ, IL-4, IL-17, and IL-22 (43). These cells are a major source of early IL-17 after pulmonary infection, and IL-17 production by these cells is regulated by IL-23 and IL-1β (44–48). γδ T-cell production of IL-10 has been shown to play a key counter-inflammatory role in some pulmonary infections such as *Pneumocystis* infection (49).

NK cells can also produce IL-4, IFNγ, and IL-17 (50) in the lung in response to infection, allergen, or ozone. One population that has been extensively studied is a population that expresses an invariant T-cell receptor (iNKT cells) that recognizes a galactolipid *Sphingomonas*, α-galactosylceramide (51, 52). These cells are elevated in the bronchial alveolar lavage fluid of patients with asthma (53, 54). NKT cells produce IFNγ in response to *S. pneumoniae* pulmonary infection (55) and IL-17 in response to *E. coli* lipopolysaccharide (LPS) (50). These cells also produce IL-17, and this response is critical for airways hyperresponsiveness to ozone (56). NK cells can develop under the control of IL-15 and express antiviral molecules such as IFN-γ as well as cytotoxic molecules (57).

Innate lymphoid cells are also important sources of effector cytokines in the lung. These cells are defined by the lack of lineage markers and T-cell receptors, but they require IL-7 signaling for their development. Thus, these cells are present in recombination-activating gene 1 (RAG1) or RAG2⁻/⁻ mice but are lacking in RAG2, common γ chain (γc) double deleted mice (58, 59). Retinoid orphan receptor γt (RORγt)-expressing cells are critical for the formation of secondary lymphoid tissues (via regulation of lymphotoxin expression) and play critical roles in mucosal immunology in the gastrointestinal tract through the production of IL-17 and IL-22 (60). Type 2 ILCs produce IL-5 and IL-13 and participate in the clearance of helminths from the gastrointestinal tract (61). These cells appear to be regulated by IL-25 (IL-17E) as well as IL-33, a member of the IL-1 family. Recently, it has been demonstrated that a population of ILCs produce IL-13 in response to IL-33 induced by viral infection, and these cells mediate in part viral induced exacerbation of allergic disease in the lung (62). These cells can also be activated by protease allergens to drive eosinphilic airways inflammation as well as airways hyperresponsiveness (58) under control of IL-33 and TSLP. Thus, these cells recapitulate many aspects of CD4+ T-cell immunity in that there are subsets that express similar effector molecules, yet these cells are activated early and their activation is independent of TCR stimulation.

CD4+ T-cell effector cytokines in the lung

Type 2 effectors

Both IL-4 and IL-13 activates STAT6 signaling in a variety of lung cells including alveolar macrophages, fibroblasts, airway smooth muscle, and airway epithelium. In macrophages, activation of STAT6 leads to what is termed 'alternative macrophage activation' which is characterized by the expression of arginase 1, YM1, YM2, and the macrophage mannose receptor (63). It has been shown that IL-4 treatment of macrophages can reduce their phagocytic ability but IL-4 stimulation of macrophages can augment the clearance of apoptotic neutrophils (63). Alternatively activated macrophages (AAMs) play regulatory roles in helminth infection and can reduce immunopathology (63). It has also been shown that AAMs have augmented dectin-1 expression as well as the macrophage mannose receptor. Given that both of these receptors are critical in recognizing the fungal carbohydrates β1,3 glucan and mannan respectively, AAMs may have greater fungicidal activity. Induction of AAMs may also be exploited by pathogens to allow their survival. For example, *Francisella tularensis*, a virulent pathogen in the lung, can prolong its intracellular survival via induction of AAMs (64).

As mentioned earlier, IL-13 induction of STAT6 signaling induces several mucin genes in airway epithelium including *Muc5ac* and *Muc5b* as well as inducing goblet cell hyperplasia (65). These signaling effects are critical for host defenses against helminths such as *Nippostrongylus brasiliensis* (66). During viral infection, airways mucins can prevent viral spread; however, in infants this can also contribute to airway obstruction. The role of IL-13 in viral infection is complex, and IL-13 is not necessarily beneficial to the host. For

example, IL-13 has recently been shown to increase the susceptibility of epithelial cells to infection with rhinovirus (67).

Type 1 effectors

There are several mechanisms by which IFN-γ controls lung immunity to intracellular pathogens. IFN-γ can prime macrophages to enhance their intracellular microbiocidal activity (68) in a process termed classical activation of macrophages (69). IFN-γ priming augments Toll-like receptor (TLR) signaling (70). IFN-γ also increases microbiocidal activity via the induction of inducible nitric oxide synthase, which regulates the production of reactive nitrogen intermediates (71, 72). IFN-γ can also increase the production of reactive oxygen species. These activities may explain the therapeutic benefit of IFN-γ in patients with chronic granulomatous disease due to mutations in NADPH oxidase (73–75).

IFN-γ signaling also upregulates class II major histocompatibility complex molecules and costimulatory molecules such as CD80 and CD86, which can augment antigen presentation to naive T cells. IFN-γ's first observed activity was its ability to suppress viral replication in many target cells including macrophages, fibroblasts, and lung epithelial cells (76). This occurs in part though the induction of many anti-viral genes such as MxA (77). However, other respiratory viruses including severe acute respiratory syndrome coronavirus are controlled by IFNγ through mechanisms that are independent of MxA (78).

IFN-γ signaling in lung structural cells including fibroblasts and epithelium cells induces several chemokine ligands for CXCR3 including CXCL9, CXCL10, and CXCL11. CXCR3 is expressed on Th1 cells, and thus, the induction of these chemokines by IFN-γ may be a critical mechanism to increase the recruitment of Th1 cells. Moreover these chemokines are critical for granuloma formation, which is essential for control of many intracellular pathogens such as *M. tuberculosis* (79, 80). Systemic and aerosolized IFN-γ has been investigated for the potential adjunctive treatment of tuberculosis. A recent meta-analysis showed that IFN-γ was well tolerated and associated with higher sputum sterilization rates (81); however, definitive randomized control trials are lacking to make firm conclusions on the efficacy of this cytokine.

Type 17 effectors

IL-17 can signal in human bronchial epithelium (HBE) to induced chemokine ligands for CXCR2 such as CXCL8, CXCL1, and the granulopoietic growth factor G-CSF (82, 83). Like other cell systems, HBE responses to IL-17 or IL-17F are augmented by TNF-α (82, 84). HBE cells express IL-17RA, IL-17RC, as well as IL-22R and IL-10R2, the receptors for IL-22 (82, 83) (Fig. 3). Since IL-17A and IL-17F can be co-expressed in the same cell, it has been reported that these two IL-17 family members can form three cytokines including IL-17A homodimers, IL-17A/F heterodimers, which have intermediate activity compared to IL-17A homodimers, and IL-17F homodimers, which have the least potent activity (85). One mechanism by which IL-17 increases the production of chemokines is through increasing mRNA stability of this transcript (86, 87) resulting in augmented protein production. A similar mechanism has also been reported for IL-17-mediated increases in G-CSF production (88).

IL-17RA is ubiquitously expressed on many cells including myeloid cells; however, these cells express very little IL-17RC. Thus, IL-17A and IL-17F have limited activity on myeloid cells. It has been reported that IL-17 can enhance IL-12p70 in alveolar macrophages (89) as well CCL2, CCL3, GM-CSF, IL-1β, and IL-9 in CD4^{+} T cells (90). Th17 cells express IL-17RA and IL-17RE, which form a receptor complex for IL-17C (91–93). IL-17C can increase the production of IL-17 by these cells (91–93). IL-17C can be expressed in lung

epithelium (unpublished observations) and thus can serve as a feed forward mechanism by which the epithelium could influence interstitial T-cell responses. In addition to regulating neutrophil recruitment in the lung (94), IL-17 augments apical bicarbonate transport in HBE cells (95). Carbonate anion regulates the activity of β defensins (96), and this may be an important mechanism of IL-17's net antimicrobial effect in the lung mucosa.

IL-17RA is required for host resistance to the extracelluar pathogens *K. pneumoniae* (94) and in this model IL-17RA regulates the local production of CXCR2 ligands as well granulopoiesis trough the regulation of G-CSF. IL-17RA is dispensable for the control of intracellular pathogen *M. tuberculosis* (83) but is required for the control of the intracellular pathogen *Franciscella tularensis* (89). In this latter model, IL-17 regulates IL-12p70 production by macrophages, which subsequently generates the Th1 CD4$^+$ T-cell response ultimately controls the pathogen (89).

IL-22 signals through STAT3 in HBE cells. IL-22 increases the clonogenic potential of HBE cells in colony assays (83) and also augments repair to puncture injury in confluent HBE cells (97) (Fig. 3). IL-17 and IL-22 stimulation of HBE and mouse tracheal epithelial cells induces several anti-microbial genes in lung epithelium including lipocalin 2 (83) and regenerating islet-derived protein 3-γ (98). Neutralization of IL-22 during experimental *K. pneumoniae* lung infection results in rapid bacteremia, which substantially increases mortality in this model. IL-22 is regulated by IL-23 and recombinant IL-22 can rescue IL-23-deficient mice (83). A complication pneumonia is acute lung injury which can be exacerbated by mechanical ventilation also called ventilation-induced lung injury (VILI). In a model of VILI, recombinant IL-22 has also been shown to decrease lung leak and improve lung fluid dynamics (99). These data support a potential therapeutic role of IL-22 in diseases such as severe pneumonia or acute respiratory distress syndrome.

In primary infection, early sources of IL-17 and IL-22 can be from innate lymphoid cells (100), NK or NKT cells (100, 101), or γδ T cells (44, 102, 103). However CD4$^+$ Th17 cells can be elicited in the lung by vaccination. Vaccine-induced Th17 responses have been shown to be play protective roles in a diverse set of organisms including both intracellular and extracellular bacteria as well as fungi. For example, Th17 cells induced by vaccination with the antigen from *M. tuberculosis* ESAT-6 induce a population of Th17 cells that augment the local production of ligands for CXCR3 in the lung and result in substantial enhanced recruitment of protective Th1 cells (104). Fungal specific Th17 cells have also been shown to be critical for vaccine-induced protection against *Coccidioides posadasii*, *Histoplasma capsulatum,* and *Blastomyces dermatitidis* infection (105). In this setting, the protection against fungal challenge was dependent on IL-17 regulation of neutrophil recruitment.

Vaccination of with whole cell polysaccharides of *S. pneumoniae* has been shown to induce IL-17 in the lung, and this IL-17 response has been shown to mediate serotype-independent immunity (106). Chen *et al.* (48) have also shown that Th17 cells elicited by *K. pneumoniae* vaccination recognize conserved outer membrane proteins in the cell wall of the bacteria and these antigens could also provide serotype-independent immunity. Th17 cells conferred heterologous protection against multiple serotypes of the organism (48). Thus in two models of important human extracelluar pathogens, Th17 cells are capable of mediating serotype independent immunity which may advance vaccine approaches against these pathogens. It still remains to be defined which specific aspects of Th17 function that are required for protection. There needs to be better understanding of factors important in generating mucosal Th17 cells in the lung such as adjuvants, factor regulating proliferation, homing and survival. More research is needed to also define the contributions of IL-22, IL-17F, and IL-17A/F heterodimers.

Conclusions

CD4^{+} T cells play critical roles in lung immunity, and these cells are impacted by many drugs as well as by HIV infection. CD4^{+} T cells are critical targets to achieve therapeutic vaccines against both bacterial and fungal pathogens. Future work will be required to understand the induction and survival of these cells in the lung and how they can be manipulated therapeutically.

Acknowledgments

References

1. Pneumocystis pneumonia--Los Angeles. MMWR Morb Mortal Wkly Rep. 1981; 30:250–252. [PubMed: 6265753]

2. Gottlieb MS, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med. 1981; 305:1425–1431. [PubMed: 6272109]

3. Masur H, et al. An outbreak of community-acquired Pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction. N Engl J Med. 1981; 305:1431–1438. [PubMed: 6975437]

4. Paul WE. What determines Th2 differentiation, in vitro and in vivo? Immunol Cell Biol. 2010; 88:236–239. [PubMed: 20157328]

5. Zhu J, et al. Conditional deletion of Gata3 shows its essential function in T(H)1-T(H)2 responses. Nat Immunol. 2004; 5:1157–1165. [PubMed: 15475959]

6. Kopf M, et al. IL-5-deficient mice have a developmental defect in CD5+ B-1 cells and lack eosinophilia but have normal antibody and cytotoxic T cell responses. Immunity. 1996; 4:15–24. [PubMed: 8574848]

7. Fallon PG, et al. IL-4 induces characteristic Th2 responses even in the combined absence of IL-5, IL-9, and IL-13. Immunity. 2002; 17:7–17. [PubMed: 12150887]

8. Dent LA, Strath M, Mellor AL, Sanderson CJ. Eosinophilia in transgenic mice expressing interleukin 5. J Exp Med. 1990; 172:1425–1431. [PubMed: 2230651]

9. Wills-Karp M, et al. Interleukin-13: central mediator of allergic asthma. Science. 1998; 282:2258–2261. [PubMed: 9856949]

10. Grunig G, et al. Requirement for IL-13 independently of IL-4 in experimental asthma. Sci. 1998; 282:2261–2263.

11. Barnes PJ. Role of GATA-3 in allergic diseases. Curr Mol Med. 2008; 8:330–334. [PubMed: 18691059]

12. Corren J. Anti-interleukin-5 antibody therapy in asthma and allergies. Curr Opin Allergy Clin Immunol. 2011; 11:565–570. [PubMed: 21971335]

13. Corren J, et al. Lebrikizumab treatment in adults with asthma. N Engl J Med. 2011; 365:1088–1098. [PubMed: 21812663]

14. Belperio JA, et al. Interaction of IL-13 and C10 in the pathogenesis of bleomycin-induced pulmonary fibrosis. Am J Respir Cell Mol Biol. 2002; 27:419–427. [PubMed: 12356575]

15. Liu T, et al. Regulation of found in inflammatory zone 1 expression in bleomycin-induced lung fibrosis: role of IL-4/IL-13 and mediation via STAT-6. J Immunol. 2004; 173:3425–3431. [PubMed: 15322207]

16. Jakubzick C, et al. Therapeutic attenuation of pulmonary fibrosis via targeting of IL-4- and IL-13-responsive cells. J Immunol. 2003; 171:2684–2693. [PubMed: 12928422]

17. Willart M, Hammad H. Lung dendritic cell-epithelial cell crosstalk in Th2 responses to allergens. Curr Opin Immunol. 2011; 23:772–777. [PubMed: 22074731]

18. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol. 1986; 136:2348–2357. [PubMed: 2419430]

19. Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell. 2000; 100:655–669. [PubMed: 10761931]

20. Wolf SF, et al. Cloning of cDNA for natural killer cell stimulatory factor, a heterodimeric cytokine with multiple biologic effects on T and natural killer cells. J Immunol. 1991; 146:3074–3081. [PubMed: 1673147]

21. Longhi MP, et al. Dendritic cells require a systemic type I interferon response to mature and induce CD4+ Th1 immunity with poly IC as adjuvant. J Exp Med. 2009; 206:1589–1602. [PubMed: 19564349]

22. Gough DJ, Levy DE, Johnstone RW, Clarke CJ. IFNgamma signaling-does it mean JAK-STAT? Cytokine Growth Factor Rev. 2008; 19:383–394. [PubMed: 18929502]

23. Dorman SE, et al. Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. Lancet. 2004; 364:2113–2121. [PubMed: 15589309]

24. Picard CJ, et al. Inherited interleukin-12 deficiency: IL12B genotype and clinical phenotype of 13 patients from six kindreds. Am J Hum Genet. 2002; 70:336–348. [PubMed: 11753820]

25. Sologuren I, et al. Partial recessive IFN-gammaR1 deficiency: genetic, immunological and clinical features of 14 patients from 11 kindreds. Hum Mol Genet. 2011; 20:1509–1523. [PubMed: 21266457]

26. Yang XO, et al. T helper 17 lineage differentiation is programmed by orphan nuclear receptors ROR alpha and ROR gamma. Immunity. 2008; 28:29–39. [PubMed: 18164222]

27. Ivanov II, et al. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell. 2006; 126:1121–1133. [PubMed: 16990136]

28. Aggarwal S, Ghilardi N, Xie MH, De Sauvage FJ, Gurney AL. Interleukin 23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin 17. J Biol Chem. 2003; 278:1910–1914. [PubMed: 12417590]

29. Harrington LE, et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol. 2005; 6:1123–1132. [PubMed: 16200070]

30. Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol. 2005; 6:1133–1141. [PubMed: 16200068]

31. Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity. 2006; 24:179–189. [PubMed: 16473830]

32. Bettelli E, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006; 441:235–238. [PubMed: 16648838]

33. Mangan PR, et al. Transforming growth factor-b induces development of the TH17 lineage. Nature. 2006; 441:231–234. [PubMed: 16648837]

34. McGeachy MJ, et al. The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo. Nat Immunol. 2009; 10:314–324. [PubMed: 19182808]

35. Veldhoen M, et al. The aryl hydrocarbon receptor links T(H)17-cell-mediated autoimmunity to environmental toxins. Nature. 2008; 453:106–109. [PubMed: 18362914]

36. Nurieva R, et al. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. Nature. 2007; 448:480–483. [PubMed: 17581589]

37. Korn T, et al. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. Nature. 2007; 448:484–487. [PubMed: 17581588]

38. Melton AC, Bailey-Bucktrout SL, Travis MA, Fife BT, Bluestone JA, Sheppard D. Expression of alphavbeta8 integrin on dendritic cells regulates Th17 cell development and experimental autoimmune encephalomyelitis in mice. J Clin Invest. 2010; 120:4436–4444. [PubMed: 21099117]

39. Acharya M, et al. alphav Integrin expression by DCs is required for Th17 cell differentiation and development of experimental autoimmune encephalomyelitis in mice. J Clin Invest. 2010; 120:4445–4452. [PubMed: 21099114]

40. Crotty S. Follicular helper CD4 T cells (TFH). Annu Rev Immunol. 2011; 29:621–663. [PubMed: 21314428]

41. Josefowicz SZ, Lu LF, Rudensky AY. Regulatory T cells: mechanisms of differentiation and function. Annu Rev Immunol. 2012; 30:531–564. [PubMed: 22224781]

42. Ray A, Khare A, Krishnamoorthy N, Qi Z, Ray P. Regulatory T cells in many flavors control asthma. Mucosal Immunol. 2010; 3:216–229. [PubMed: 20164832]

43. Bonneville M, O'Brien RL, Born WK. Gammadelta T cell effector functions: a blend of innate programming and acquired plasticity. Nat Rev Immunol. 2010; 10:467–478. [PubMed: 20539306]

44. Lockhart E, Green AM, Flynn JL. IL-17 production is dominated by gammadelta T cells rather than CD4 T cells during Mycobacterium tuberculosis infection. J Immunol. 2006; 177:4662–4669. [PubMed: 16982905]

45. Shibata K, Yamada H, Hara H, Kishihara K, Yoshikai Y. Resident Vdelta1+ gammadelta T cells control early infiltration of neutrophils after Escherichia coli infection via IL-17 production. J Immunol. 2007; 178:4466–4472. [PubMed: 17372004]

46. Sutton CE, Lalor SJ, Sweeney CM, Brereton CF, Lavelle EC, Mills KH. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity. Immunity. 2009; 31:331–341. [PubMed: 19682929]

47. Martin B, Hirota K, Cua DJ, Stockinger B, Veldhoen M. Interleukin-17-producing gammadelta T cells selectively expand in response to pathogen products and environmental signals. Immunity. 2009; 31:321–330. [PubMed: 19682928]

48. Chen K, et al. Th17 cells mediate clade-specific, serotype-independent mucosal immunity. Immunity. 2011; 35:997–1009. [PubMed: 22195749]

49. Steele CR, Oppenheim DE, Hayday AC. Gamma(delta) T cells: non-classical ligands for non-classical cells. Curr Biol. 2000; 10:R282–R285. [PubMed: 10753741]

50. Michel ML, et al. Identification of an IL-17-producing NK1.1neg iNKT cell population involved in airway neutrophilia. J Exp Med. 2007

51. Brossay L, et al. CD1d-mediated recognition of an alpha-galactosylceramide by natural killer T cells is highly conserved through mammalian evolution. J Exp Med. 1998; 188:1521–1528. [PubMed: 9782129]

52. Burdin N, et al. Selective ability of mouse CD1 to present glycolipids: alpha-galactosylceramide specifically stimulates V alpha 14+ NK T lymphocytes. J Immunol. 1998; 161:3271–3281. [PubMed: 9759842]

53. Akbari O, et al. CD4+ invariant T-cell-receptor+ natural killer T cells in bronchial asthma. N Engl J Med. 2006; 354:1117–1129. [PubMed: 16540612]

54. Pettersson B, Curvall M, Enzell C. The inhibitory effect of tobacco smoke compound on ciliary activity. Eur J Respir Dis. 1985; 139(Suppl):89–92.

55. Nakamatsu M, et al. Role of interferon-gamma in Valpha14+ natural killer T cell-mediated host defense against Streptococcus pneumoniae infection in murine lungs. Microbes Infect. 2007; 9:364–374. [PubMed: 17314060]

56. Pichavant M, et al. Ozone exposure in a mouse model induces airway hyperreactivity that requires the presence of natural killer T cells and IL-17. J Exp Med. 2008; 205:385–393. [PubMed: 18250191]

57. Steel JC, Waldmann TA, Morris JC. Interleukin-15 biology and its therapeutic implications in cancer. Trends Pharmacol Sci. 2012; 33:35–41. [PubMed: 22032984]

58. Halim TY, Krauss RH, Sun AC, Takei F. Lung natural helper cells are a critical source of th2 cell-type cytokines in protease allergen-induced airway inflammation. Immunity. 2012; 36:451–463. [PubMed: 22425247]

59. Spits H, Cupedo T. Innate lymphoid cells: emerging insights in development, lineage relationships, and function. Annu Rev Immunol. 2012; 30:647–675. [PubMed: 22224763]

60. Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity. 2008; 28:454–467. [PubMed: 18400188]

61. Neill DR, McKenzie AN. Nuocytes and beyond: new insights into helminth expulsion. Trends Parasitol. 2011; 27:214–221. [PubMed: 21292555]

62. Kim HY, et al. Innate lymphoid cells responding to IL-33 mediate airway hyperreactivity independently of adaptive immunity. J Allergy Clin Immunol. 2012; 129:216–227. [PubMed: 22119406]

63. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. Immunity. 2010; 32:593–604. [PubMed: 20510870]

64. Shirey KA, Cole LE, Keegan AD, Vogel SN. Francisella tularensis live vaccine strain induces macrophage alternative activation as a survival mechanism. J Immunol. 2008; 181:4159–4167. [PubMed: 18768873]

65. Rose MC, Piazza FM, Chen YA, Alimam MZ, Bautista MV, Letwin N, et al. Model systems for investigating mucin gene expression in airway diseases. J Aerosol Med. 2000; 13:245–261. [PubMed: 11066028]

66. Price AE, et al. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. Proc Natl Acad Sci USA. 2010; 107:11489–11494. [PubMed: 20534524]

67. Lachowicz-Scroggins ME, Boushey HA, Finkbeiner WE, Widdicombe JH. Interleukin-13-induced mucous metaplasia increases susceptibility of human airway epithelium to rhinovirus infection. Am J Respir Cell Mol Biol. 2010; 43:652–661. [PubMed: 20081054]

68. Murray HW. Interferon-gamma, the activated macrophage, and host defense against antimicrobial challenge. Ann Int Med. 1988; 108:595–608. [PubMed: 3126690]

69. Gordon S. Alternative activation of macrophages. Nat Rev Immunol. 2003; 3:23–35. [PubMed: 12511873]

70. Schroder K, Sweet MJ, Hume DA. Signal integration between IFNgamma and TLR signalling pathways in macrophages. Immunobiology. 2006; 211:511–524. [PubMed: 16920490]

71. Xie QW, et al. Cloning and characterization of inducible nitric oxide synthase from mouse macrophages. Science. 1992; 256:225–228. [PubMed: 1373522]

72. Xie QW, Whisnant R, Nathan C. Promoter of the mouse gene encoding calcium-independent nitric oxide synthase confers inducibility by interferon gamma and bacterial lipopolysaccharide. J Exp Med. 1993; 177:1779–1784. [PubMed: 7684434]

73. Naderi BF, et al. Increased production of nitric oxide by neutrophils from patients with chronic granulomatous disease on interferon-gamma treatment. Int Immunopharmacol. 2012; 12:689–693. [PubMed: 22330085]

74. Segal BH, Veys P, Malech H, Cowan MJ. Chronic granulomatous disease: lessons from a rare disorder. Biol Blood Marrow Transplant. 2011; 17:S123–S131. [PubMed: 21195301]

75. Fernandez-Boyanapalli R, et al. Impaired phagocytosis of apoptotic cells by macrophages in chronic granulomatous disease is reversed by IFN-gamma in a nitric oxide-dependent manner. J Immunol. 2010; 185:4030–4041. [PubMed: 20805415]

76. Hovanessian AG, La BC, Falcoff E. Action of murine gamma (immune)interferon on beta (fibroblast)-interferon resistant L 1210 and embryonal carcinoma cells. J Interferon Res. 1980; 1:125–135. [PubMed: 6180035]

77. Ronni T, Sareneva T, Pirhonen J, Julkunen I. Activation of IFN-alpha, IFN-gamma, MxA, and IFN regulatory factor 1 genes in influenza A virus-infected human peripheral blood mononuclear cells. J Immunol. 1995; 154:2764–2774. [PubMed: 7876547]

78. Spiegel M, Pichlmair A, Muhlberger E, Haller O, Weber F. The antiviral effect of interferon-beta against SARS-coronavirus is not mediated by MxA protein. J Clin Virol. 2004; 30:211–213. [PubMed: 15135736]

79. Aly S, Laskay T, Mages J, Malzan A, Lang R, Ehlers S. Interferon-gamma-dependent mechanisms of mycobacteria-induced pulmonary immunopathology: the role of angiostasis and CXCR3-targeted chemokines for granuloma necrosis. J Pathol. 2007; 212:295–305. [PubMed: 17534845]

80. Chakravarty SD, Xu J, Lu B, Gerard C, Flynn J, Chan J. The chemokine receptor CXCR3 attenuates the control of chronic Mycobacterium tuberculosis infection in BALB/c mice. J Immunol. 2007; 178:1723–1735. [PubMed: 17237422]

81. Gao XF, Yang ZW, Li J. Adjunctive therapy with interferon-gamma for the treatment of pulmonary tuberculosis: a systematic review. Int J Infect Dis. 2011; 15:e594–e600. [PubMed: 21715206]

82. McAllister F, et al. Role of IL-17A, IL-17F, and the IL-17 Receptor in Regulating Growth-Related Oncogene-{alpha} and Granulocyte Colony-Stimulating Factor in Bronchial Epithelium: Implications for Airway Inflammation in Cystic Fibrosis. J Immunol. 2005; 175:404–412. [PubMed: 15972674]

83. Aujla SJ, et al. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med. 2008; 14:275–281. [PubMed: 18264110]

84. Jones CE, Chan K. Interleukin-17 stimulates the expression of interleukin-8, growth-related oncogene-alpha, and granulocyte-colony-stimulating factor by human airway epithelial cells. Am J Respir Cell Mol Biol. 2002; 26:748–753. [PubMed: 12034575]

85. Wright JF, et al. Identification of an interleukin 17F/17A heterodimer in activated human CD4+ T cells. J Biol Chem. 2007; 282:13447–13455. [PubMed: 17355969]

86. Hartupee J, Liu C, Novotny M, Li X, Hamilton T. IL-17 enhances chemokine gene expression through mRNA stabilization. J Immunol. 2007; 179:4135–4141. [PubMed: 17785852]

87. Sun D, Novotny M, Bulek K, Liu C, Li X, Hamilton T. Treatment with IL-17 prolongs the half-life of chemokine CXCL1 mRNA via the adaptor TRAF5 and the splicing-regulatory factor SF2 (ASF). Nat Immunol. 2011; 12:853–860. [PubMed: 21822258]

88. Cai XY, Gommoll CPJ, Justice L, Narula SK, Fine JS. Regulation of granulocyte colony-stimulating factor gene expression by interleukin-17. Immunol Lett. 1998; 62:51–58. [PubMed: 9672148]

89. Lin Y, et al. Interleukin-17 is required for T helper 1 cell immunity and host resistance to the intracellular pathogen Francisella tularensis. Immunity. 2009; 31:799–810. [PubMed: 19853481]

90. Ishigame H, Kakuta S, Nagai T, Kadoki M, Nambu A, Komiyama Y, et al. Differential roles of interleukin-17A and -17F in host defense against mucoepithelial bacterial infection and allergic responses. Immunity. 2009; 30:108–119. [PubMed: 19144317]

91. Song X, et al. IL-17RE is the functional receptor for IL-17C and mediates mucosal immunity to infection with intestinal pathogens. Nat Immunol. 2011; 12:1151–1158. [PubMed: 21993849]

92. Ramirez-Carrozzi V, et al. IL-17C regulates the innate immune function of epithelial cells in an autocrine manner. Nat Immunol. 2011; 12:1159–1166. [PubMed: 21993848]

93. Chang SH, Reynolds JM, Pappu BP, Chen G, Martinez GJ, Dong C. Interleukin-17C promotes Th17 cell responses and autoimmune disease via interleukin-17 receptor E. Immunity. 2011; 35:611–621. [PubMed: 21982598]

94. Ye P, et al. Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. J Exp Med. 2001; 194:519–527. [PubMed: 11514607]

95. Kreindler JL, et al. Interleukin-17A induces bicarbonate secretion in normal human bronchial epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2009; 296:L257–L266. [PubMed: 19074559]

96. Dorschner RA, et al. The mammalian ionic environment dictates microbial susceptibility to antimicrobial defense peptides. FASEB J. 2006; 20:35–42. [PubMed: 16394265]

97. Aujla SJ, Kolls JK. IL-22: a critical mediator in mucosal host defense. J Mol Med. 2009; 87:451–454. [PubMed: 19219418]

98. Zheng Y, et al. Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. Nat Med. 2008; 14:282–289. [PubMed: 18264109]

99. Hoegl S, et al. Protective Properties of Inhaled IL-22 in a Model of Ventilator-induced Lung Injury. Am J Respir Cell Mol Biol. 2011; 44:369–376. [PubMed: 20463292]

100. Crellin NK, Trifari S, Kaplan CD, Cupedo T, Spits H. Human NKp44+IL-22+ cells and LTi-like cells constitute a stable RORC+ lineage distinct from conventional natural killer cells. J Exp Med. 2010; 207:281–290. [PubMed: 20142432]

101. Cella M, et al. A human natural killer cell subset provides an innate source of IL-22 for mucosal immunity. Nature. 2009; 457:722–725. [PubMed: 18978771]

102. Shibata K, Yamada H, Hara H, Kishihara K, Yoshikai Y. Resident Vdelta1+ gammadelta T cells control early infiltration of neutrophils after Escherichia coli infection via IL-17 production. J Immunol. 2007; 178:4466–4472. [PubMed: 17372004]

103. Simonian PL, Roark CL, Born WK, O'Brien RL, Fontenot AP. Gammadelta T cells and Th17 cytokines in hypersensitivity pneumonitis and lung fibrosis. Transl Res. 2009; 154:222–227. [PubMed: 19840763]

104. Khader SA, et al. IL-23 and IL-17 in the establishment of protective pulmonary CD4+ T cell responses after vaccination and during Mycobacterium tuberculosis challenge. Nat Immunol. 2007; 8:369–377. [PubMed: 17351619]

105. Wuthrich M, et al. Vaccine-induced protection against 3 systemic mycoses endemic to North America requires Th17 cells in mice. J Clin Invest. 2011; 121:554–568. [PubMed: 21206087]

106. Malley R, et al. Antibody-independent, interleukin-17A-mediated, cross-serotype immunity to pneumococci in mice immunized intranasally with the cell wall polysaccharide. Infect Immun. 2006; 74:2187–2195. [PubMed: 16552049]
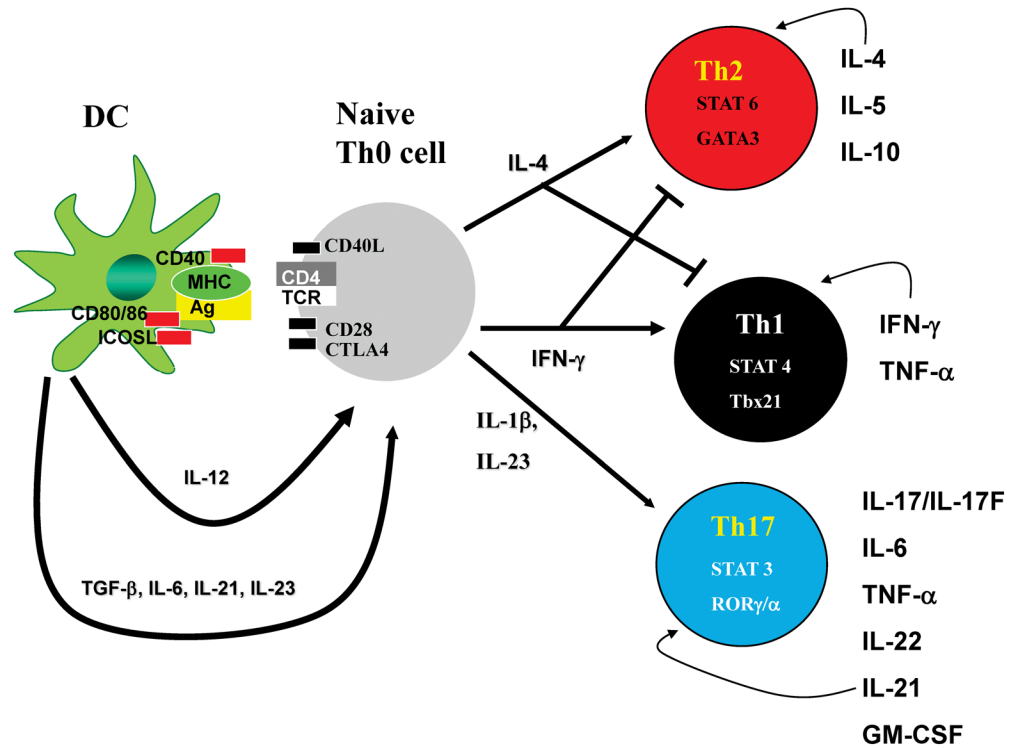
Fig. 1. CD4^{+} T-helper cell differentiation
Antigen is presented by dendritic cells (DCs) by class II major histocompatibility complex (MHC) to naive CD4^{+} Th0 cells. Full T-cell activation requires a second signal consisting of the upregulation and expression of costimulatory molecules such as inducible costimulatory ligand (ICOSL), CD28, and cytotoxic T-lymphocyte antigen-4 (CTLA-4). T-cell differentiation is instructed by cytokine/growth factor signals. Tbet can be activated by STAT1 as well as bind to the IFNγ locus followed by induction of IL-12βR2. IL-12 activates STAT4, which can further drive Th1 development. IFNγ can act in an autocrine manner to further augment Th1 differentiation. IL-4 induces Gata3, which further induces IL-4 and supports the differentiation of Th2 cells. Th2 cells produce IL-4, IL-5, and IL-13 as their effector cytokines. TGFβ and IL-6 can induce RORγt expression as well as activation of STAT3. This leads to induction of the IL-23 receptor, rendering these cells responsive to IL-23, which is required for terminal differentiation of Th17 cells. Th17 cells produce the cytokines IL-17/IL-17F, IL-22, IL-21. IL-21 can act in an autocrine fashion to further the differentiation of the Th17 lineage.
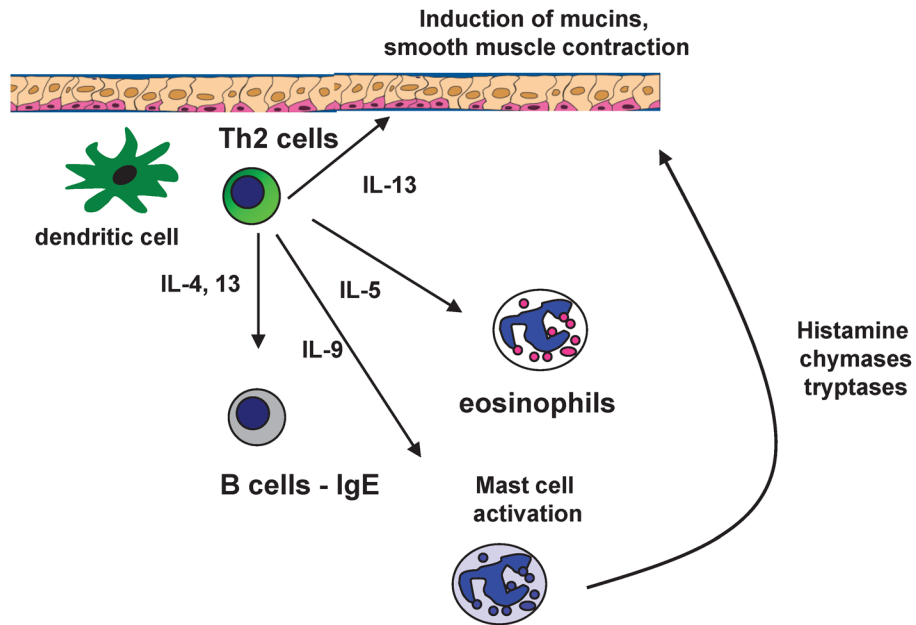
Fig. 2. Th2 cells and immunity at the mucosa
Allergen parasites or helminthic infection can induce TSLP and IL-25 in the lung epithelium. These cytokines can drive early IL-4 production leading to the differentiation of Th2 cells. IL-4 and IL-13 can drive the induction of IgE as well as stimulate epithelial cells to increase mucous production. IL-5 is a critical regulator of eosinophilopoiesis. Binding of IgE to FcRε on mast cells leads to their degranulation and release of chymases, tryptases, and histamines.
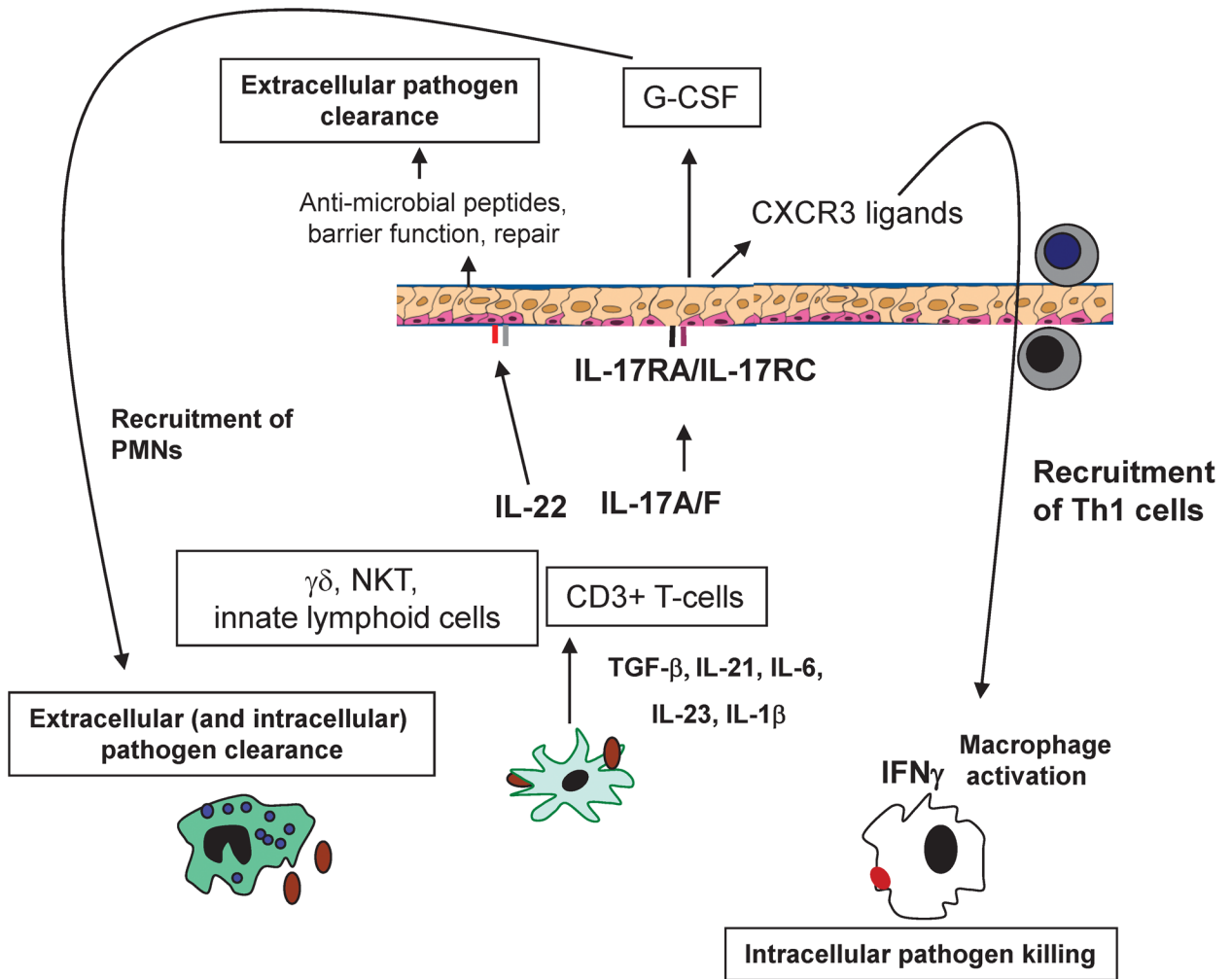
Fig. 3. Th17 cytokines in mucosal immunity
Many infections, including those caused by fungi and bacteria, can activate dendritic cells and macrophages to produce IL-6, IL-23, and IL-1β. IL-23 and IL-1β can drive IL-17 production by both innate lymphoid cells and γδ T-cells. Differentiation of Th17 cells requires TGFβ, and a critical mechanism of activation of TGFβ in the lung is through the activation of this growth factor by αv inetgrins. IL-17 and IL-22 can signal to the epithelium to augment G-CSF as well as ligands for CXCR2 that mediate the recruitment of neutrophils. These two cytokines also induce the expression of antimicrobial proteins such as lipcolain-2 and β-defensins. IL-22 can also augment epithelial repair. After vaccination, Th17 cells through the production of IL-17 can also induce ligands for CXCR3 that increase the recruitment of IFNγ–producing Th1 cells, which can also help control intracellular pathogen growth.