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Host defenses against bacterial lower respiratory tract infection

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Abstract

Bacterial pneumonia continues to be a significant cause of morbidity and mortality worldwide. Recent studies have shown that lung epithelia signal through pattern recognition receptors to initiate the innate immune response. Other mediators of innate immunity against bacterial pneumonia include transepithelial dendritic cells, alveolar macrophages, and innate produces of IL-17. CD4+ T cells and B cells play a key role in eliminating and preventing the development of bacterial pneumonias. B cell development and maturation can be modulated by the lung epithelia through BAFF and APRIL, furthering our current understanding of the role of epithelial cells in the immune response.

Introduction

Bacterial pneumonia is the leading cause of childhood mortality in the world, accounting for approximately 1.6 million deaths in children younger than five years old in 2008 [1]. While developing countries have the highest burden of mortality, developed countries still struggle with providing adequate treatment. Although antibiotics are the first-line treatment, a recent study in the UK demonstrated that 61% of children hospitalized with pneumonia failed to receive antibiotics prior to hospitalization [2]. Furthermore, potentially life-saving therapies such as transplantation, immunosuppression, and chemotherapies make individuals susceptible to opportunistic infections, such as pneumonias [3]. In addition, immuno-compromised patients, such as those with HIV, are also at high risk for developing pneumonia. Thus, lower respiratory tract infections continue to be the leading cause of intensive care unit admissions in patients with HIV [4].

Pneumonias are typically classified as either community-acquired or hospital-acquired; this distinction is appropriate, as the two conditions tend to differ in terms of clinical presentation, pathogenesis, and treatment. Community-acquired pneumonia (CAP) affects 5–6 million in the United States a year, resulting in more than one million hospitalizations [5]. CAP is typically caused by antibiotic-sensitive strains of *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* [6,7]. However, hospital-acquired pneumonia (HAP) is more commonly caused by multi-drug resistant strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. HAP is one of the most prevalent nosocomial infections; one prospective study showed approximately 7% of ICU patients developed nosocomial pneumonia, with increased length of stay and mechanical ventilation as the greatest risk factors [8].

The common pathogens causing bacterial pneumonia and their interactions with the host's defenses, both innate and adaptive, will be discussed in the present review.

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Innate immunity

Innate immunity is orchestrated by several key cells in the lung. The cells that make up the respiratory epithelium vary in terms of morphology and gene expression as one moves down from the trachea to the respiratory bronchiole. Three major cell types line the airway: the ciliated cell, the mucous secreting goblet cell, and the secretory Clara cell. In addition, in the upper airways, there are submucosal glands that contribute to airway secretions. It remains controversial at present if the lung below the glottis is sterile or if there is a lung microbiome. However, it is clear that if there is a normal microbial constituency in the lower respiratory tract it pales in comparison to that in the gastrointestinal tract. One of the most critical components of innate immunity however is the sophisticated structure of the epithelium that can move inhaled or aspirated bacterial out of the lung through mucociliary transport [9,10]. Significantly, disruption in this process such as the immotile cilia syndromes [10] can lead to chronic lower respiratory bacterial infection and the development of bronchiectasis. Moreover, defects in chloride conductance across the epithelium/submucosal glands through mutations in CFTR leads to cystic fibrosis which is characterized by chronic bacterial colonization and bronchiectasis as well [11]. These two diseases in humans clearly implicate the critical role of the epithelium in coordinating innate immunity in terms of mediating ion transport and ciliary clearance. In addition to the epithelium, the major resident myeloid derived cells are airway and alveolar macrophages. These cells can mediate both opsonic and nonopsonic phagocytosis of inhaled or aspirated pathogens.

In the alveolar space, these cells interact with surfactant proteins, A, B, C, and D. These proteins are secreted by Type II airway epithelial cells and are components of surfactant which is critical in reducing surface tension in the alveoli [12,13]. However, surfactant proteins A and D are members of the collagen containing C-type lectins (collectins) and function as pattern recognition receptors (PRRs) in the lower airway. A review of these proteins has recently been published [13,14].

Many recent studies have focused on the ability of respiratory epithelium to respond to pathogens through PRRs such as Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs). Most TLRs (TLR1–6, 9) are found on respiratory epithelium and the function of TLRs in response to several pathogens resulting in lower respiratory infection has been well characterized (Table 1) [15–17]. Signaling through TLR2, which recognizes bacterial peptidoglycans and lipoproteins, appears to be crucial for host response to both extracellular (*S. pneumoniae, P. aeruginosa, S. aureus*) and intracellular bacteria (*L. pneumophila, C. pneumoniae, M. pneumoniae*) [15,16,18,19]. TLRs may also be potential vaccine targets, as prophylactic stimulation of TLR5 with *Salmonella enterica* flagellin increased survival upon subsequent challenge with *S. pneumoniae* [20].

Along with TLRs, cytosolic NLRs appear to be another means for epithelial cells to recognize invading bacteria. Two NLR family members, neuronal apoptosis inhibitory protein 4 (NAIP4) and ICE protease-activating factor (IPAF), appear to be crucial in recognizing *L. pneumophila* flagellin and restricting bacterial replication within human macrophages and epithelium [21]. NLR-dependent signals are also able to modulate and enhance the immune response. In response to pneumococcal peptidoglycan, NOD2 signaling stimulates the production of CCL2, recruiting macrophages and neutrophils to the site of infection [22]. Mice lacking NLRP3 signaling failed to secrete IL-1β and subsequently had an increased bacterial burden and greater mortality following *C. pneumoniae* infection in the lung [23]. The NLRs that recognize other bacterial pathogens can be found in Table 1.

Most TLR and NLR signaling cascades within airway epithelium result in the release of chemokines (GM-CSF, MIP-2, KC, etc.), thereby allowing the epithelium to modulate the inflammatory response (Figure 1) [23]. Other innate immune cells, such as transepithelial dendritic cells and alveolar macrophages, can also modify the cytokine milieu in response to TLR signaling. Roses *et al*. demonstrated that *in vitro* stimulation of dendritic cells with a single agonist to TLR2, 4, or 7/8 resulted in the production of IL-23, while IL-12 release was seen upon stimulation with the same agonists applied in combination or with IFN-γ [24]. Both TLR4 and 9 activation also appears to contribute to the production of IL-23 by dendritic cells following *in vivo* infection by *K. pneumoniae* [25,26].

IL-23 is a potent activator of innate producers of the IL-17, such as γ/δ T cells, invariant natural killer T (iNKT) cells, and lymphoid tissue inducer like (LTi-like) cells. Stimulation of γ/δ T cells with TLR2 agonists in the presence of IL-23 led to early expansion of IL-17^{+} γ/δ T cells, suggesting that γ/δ T cells are one of the earliest producers of IL-17 in response to infection [27••,28••,29–31]. In fact, this has been recently shown for pulmonary *K. pneumoniae* infection [31]. Lung γ/δ T cells express both IL-23 receptors, as well as high levels of IL-1R1 and IL-1b, which can increase IL-17 production by these cells *in vitro* and *in vivo* [29,32]. iNKT cells have also been implicated in innate lung immunity, using different signaling pathways for different antigens. Influenza A virus stimulated IL-22 and IFN-γ release through a CD1d-dependent mechanism, while iNKT cells responded to Staphylococcal enterotoxin B in a CD1d-independent manner [33,34]. Furthermore, LTi-like cells constitutively express IL-23R and release IL-17 and IL-22 upon stimulation with zymosan [35].

IL-17R signaling has been shown to regulate local G-CSF and CXC chemokine expression in the lung in acute Gram negative bacterial pneumonia [36•] and the principal ligand of this activity is likely IL-17A [37]. However, human lung epithelium express both IL-17RA and IL-17RC [38,39] and IL-17F can also stimulate G-CSF expression as well as induce CXC chemokines such as CXCL1 [38]. IL-22R and IL-10R2 are also expressed by human and murine lung epithelium [37] and can increase the clonogenic potential of these cells to form colonies in a limiting dilution assay [37]. Moreover, IL-22 can accelerate wound repair in human bronchial epithelial cells in a puncture wound assay [37]. IL-22 is induced in the lung in response to Gram negative pneumonia and requires IL-23 [37]. Neutralization of IL-22 during gram-negative pneumonia results in rapid bacteremia and increased mortality [37]. Recombinant IL-22 induces the expression of epithelial antimicrobial genes such as lipocalin-2 and reduces bacterial burden in the lung during pneumonia [37]. IL-22 can activate STAT3 in human lung epithelial cells and likely works in combination with other cytokines such as IL-17 and TNF to increase the expression of antimicrobial genes in lung epithelium. Moreover, IL-22 may have therapeutic potential in severe multi-lobar pneumonia which can have a high mortality. A complication of pneumonia is respiratory failure and thus the need for mechanical ventilation. This can result in ventilator-induced lung injury (VILI) characterized by increased vascular leak and lung barotrauma. Recombinant IL-22 has recently been shown to be therapeutic in VILI by reducing edema in the lung and bio-markers of barotrauma [40].

Bacterial pneumonia due to both *S. pneumoniae* and *S. aureus* are a known complication of influenza infection [41,42•]. Recently this has been successfully modeled in experimental rodents and several immunological mechanisms have been proposed but all of these models support impairment of pulmonary innate immunity as a common theme. Influenza infection leads to the induction of the type II interferon, interferon-γ, which markedly downregulates the expression of the scavenger receptor MARCO in alveolar macrophages [43]. Impairment of MARCO expression leads to reduced uptake and phagocytic killing of the organisms [43]. Influenza also induces the expression of Type I IFNs which can suppress the

expression of CXC chemokine genes critical for neutrophil recruitment and killing of *S. pneumoniae* [44]. Influenza can also markedly impair host defense against *S. aureus* infection by the induction of type I interferons which suppress IL-23 producing by lung macrophages and dendritic cells, impairing the subsequent type 17 cytokine response [45]. By understanding these defects in innate immunity, it is hoped that we can prevent morbidity and mortality of influenza as a major cause of morbidity and mortality is secondary bacterial pneumonia.

Adaptive immunity

Adaptive immunity plays a critical role in pulmonary immunity to many pathogens and is the increasing focus of vaccine induced immunity. As CD8+ T-cell immunity plays a limited role in most bacterial infections, we will focus on CD4+ and humoral immunity in this review. The critical role of CD4+ T-cells in orchestrating pulmonary immunity has been clearly illustrated by the HIV epidemic. As HIV infection progresses to AIDS through the depletion of CD4+ T-cells, the lung is a prevalent site of opportunistic infection including *Pneumocystis jirovecii*, Cryptococcal infection and bacterial pneumonia. In fact, patients with HIV infection have much higher rates of bacteremia suggesting that CD4+ T-cell immunity may also play a key role in containment of infection.

CD4+ T-cells

CD4+ T-cells differentiate from naïve precursors into several subsets upon receiving a T-cell receptor signal from a class II restricted antigen. Differentiation of T-cells requires co-stimulatory signals from antigen presenting cells and cytokine signals [46]. The first two subsets described were termed Th1 which develop under interferon-γ and Th2 cells which develop under IL-4 [47]. Th1 cells develop under the transcription factors TBX21, EOMES, and STAT4 [48]. One of the key effector cytokines produced by Th1 cells is interferon-γ which plays critical roles in controlling the growth of intracellular pathogens such as *M. tuberculosis* [49•,50•]. Interferon-γ can increase microbiocidal activity of macrophages by increasing both reactive oxygen species as well as reactive nitrogen intermediates. Interferon-γ also markedly increases Class II major histocompatibility complex expression as well [51,52]. In lung parenchymal and epithelial cells, interferon receptor signaling can result in the expression of CXCL9, CXCL10, and CXCL11 [53] which are all ligands for CXCR3 expressed on Th1 cells. This provides a mechanism of how pulmonary Th1 cells can augment their own recruitment which may be critical to form complex immune responses such as granuloma formation [54]. Humans with mutations in interferon or interferon receptor signaling are highly susceptible to intracellular infections such as TB and disseminated BCG infection [55].

Th2 cells develop under the control of the transcription factors GATA3 and STAT6 and express IL-4, IL-5, and IL-13. IL-5 regulates eosinophilopoiesis and IL-13 can increase the expression of Muc5AC, Muc5AB and mediate goblet cell hyperplasia in the airway [56]. These pathways are thought to be critical for controlling helminth infection [57]. IL-4 is critical for B-cell proliferation and upregulation of class II MHC, as well as class switching to IgE and IgG4 production. Polysaccharide vaccines such as Pneumococcal vaccine are T-cell independent and result in IgG responses independent of CD4+ T-cell help [58••]. However these vaccines are poorly immunogenic in young childhood and this has led to the development of conjugate vaccines where polysaccharides are conjugated to Diphtheria proteins [59] allowing these vaccines to activate T-cell immunity even in young children. The precise role of Th2 immunity in the response to these vaccines remains to be defined but polymorphisms in IL-4 have been associated with reduced antibody titers in vaccinees [60].

A conundrum of the HIV epidemic was the marked susceptibility to the fungal pneumonia *Pneumocystis* but mice with defective Th1 or Th2 immunity were not susceptible to infection suggesting other effector populations in the lung. IL-17 producing cells appeared to be a good candidate as IL-17 is induced in the lung in response to both bacterial and fungal infections [61] and early studies showed that IL-17 producing T-cells were distinct from Th1 cells and co-expressed TNF-α and GMCSF [62]. Th17 cells develop under the control of RORA, RORC and STAT3 [63•,64•,65]. Patients with mutations in STAT3 develop hyper IgE syndrome (HIES) and fail to develop antigen specific Th17 cells in response to *C. albicans* or *S. aureus* [66••,67]. These patients develop cutaneous infection as well pulmonary infection with *S. aureus* as well chronic mucocutaneous candidiasis. A recent study by Minegishi showed the T-cell supernatants from HIES fail to make IL-17 or IL-22 and failed to induce a number of defensins in skin keratinocytes or lung epithelium [68]. There has also been case reports of *Pneumocystis* infections in HIES patients [69,70]. It has been hypothesized that Th17 cells are critical in regulating the expression of both chemokines and anti-microbial proteins in the lung that are critical for mucosal immunity against extracellular pathogens [61]. To this end, IL-17 evolutionarily predates T-cell ontogeny with IL-17D orthologs being present in organisms such as oyster and *Ciona intestinalis* that lack T-cells [31]. In fact, IL-17A and IL-17F co-evolved with recombinase activating (RAG) genes suggesting an evolutionary advantage of T-cell expressed IL-17A and IL-17F. One possibility is that Th17 cells afford aspects of pulmonary immunity that other T-cell subsets or humoral immunity cannot provide. It is important to keep in mind that some of the most successful agents that cause pneumoniae are polysaccharide encapsulated organisms such as *S. pneumoniae* or *K. pneumoniae*. Capsular antibody responses are restricted to the capsular serotype of the organism and thus would limit the immunity to that capsular strain. However, Th17 cells can be generated to conserved outer membrane proteins in the instance of *K. pneumoniae* and this response confers broader clade specific immunity [31]. Similar responses have also been observed with *S. pneumoniae* where IL-17 could achieve serotype independent immunity [58••]. Thus, this boarder specificity of the Th17 response may have conferred a host advantage to contend with encapsulated bacteria that can alter surface polysaccharide as major virulence mechanism.

A recently identified fourth effector is T follicular helper (Tfh) cells which develop under control of the transcription factor BCL6 and IL-21 [71]. A critical subpopulation of these cells reside in germinal centers, upregulate CD40L as well as ICOS and mediate antigen presentation to B-cells as well facilitate class switching. IL-21 also serves as a growth factor for B-cells. Thus, Tfh cells are likely critical to generate mucosal class switched antibody responses to T-cell dependent antigens [71] and may be critical cells to target for mucosal vaccines.

Humoral immunity

Humoral immunity plays key roles in preventing bacterial pneumonia in the lung. Patients with defects in humoral immunity such as common variable immunodeficiency (CVID) are associated with increased risk of pulmonary infections due to encapsulated bacteria [72]. The mainstay of treatment of these disorders is to provide IgG replacement with intravenous immunoglobulin (IVIG) and this therapy is quite effective in alleviating the pulmonary complications of CVID. As mentioned above, a major site of initial B-cell class switching is in the germinal centers of draining lymphoid tissue. However it has been demonstrated that the lung epithelium can also express molecules important in B-cell survival and class switching such as APRIL and BAFF and thus some humoral responses may be generated at the mucosa (Figure 1) [73]. Additionally, lung epithelial cells express the polymeric immunoglobulin receptor and transport IgA into the airway lumen [74]. As nearly all of the current vaccines prevent pneumonia via the generation of antibodies, it will be important to

fully understand the generation of humoral responses in the lung. Indeed recently it has been shown that IL-17 can induce the expression of polymeric immunoglobulin receptor [37] and facilitate IgA transport [75].

Conclusions

The first lines of immunity against lower respiratory tract bacterial infection are cells of the innate immune system including macrophages and epithelial cells. Recently innate lymphoid cells and gamma delta T-cells have also been implicated in pneumonia and these cells can secrete effector cytokines analogous to cells belonging to the adaptive T-cell lineages. These cells may serve to augment mucosal immunity prior to initiation of adaptive immunity. It will be important to understand the activation of these cells, the signals that control their expansion and contraction as well as the target cells of their effector molecules.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest

•• of outstanding interest

1. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, Jha P, Campbell H, Walker CF, Cibulskis R, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010; 375:1969–1987. [PubMed: 20466419]
2. Grant CC, Harnden A, Mant D, Emery D, Coster G. Why do children hospitalised with pneumonia not receive antibiotics in primary care? Arch Dis Child. 2012; 97:21–27. [PubMed: 22100740]
3. Sanders KM, Marras TK, Chan CK. Pneumonia severity index in the immunocompromised. Can Respir J. 2006; 13:89–93. [PubMed: 16550266]
4. Adlakha A, Pavlou M, Walker DA, Copas AJ, Dufty N, Batson S, Edwards SG, Singer M, Miller RF. Survival of HIV-infected patients admitted to the intensive care unit in the era of highly active antiretroviral therapy. Int J STD AIDS. 2011; 22:498–504. [PubMed: 21890545]
5. Corrales-Medina VF, Suh KN, Rose G, Chirinos JA, Doucette S, Cameron DW, Fergusson DA. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. PLoS Med. 2011; 8:e1001048. [PubMed: 21738449]
6. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis. 2011; 52(Suppl. 4):S296–S304. [PubMed: 21460288]
7. Meatherall BL, Gregson D, Ross T, Pitout JD, Laupland KB. Incidence, risk factors, and outcomes of *Klebsiella pneumoniae* bacteremia. Am J Med. 2009; 122:866–873. [PubMed: 19699383]
8. Alp E, Guven M, Yildiz O, Aygen B, Voss A, Doganay M. Incidence, risk factors and mortality of nosocomial pneumonia in intensive care units: a prospective study. Ann Clin Microbiol Antimicrob. 2004; 3:17. [PubMed: 15369593]
9. Toczylowska-Maminska R, Dolowy K. Ion transporting proteins of human bronchial epithelium. J Cell Biochem. 2012; 113:426–432. [PubMed: 21975871]
10. Sagel SD, Davis SD, Campisi P, Dell SD. Update of respiratory tract disease in children with primary ciliary dyskinesia. Proc Am Thorac Soc. 2011; 8:438–443. [PubMed: 21926396]
11. Callaghan M, McClean S. Bacterial host interactions in cystic fibrosis. Curr Opin Microbiol. 2012; 15:71–77. [PubMed: 22137884]

12. Dietl P, Haller T. Exocytosis of lung surfactant: from the secretory vesicle to the air-liquid interface. Annu Rev Physiol. 2005; 67:595–621. [PubMed: 15709972]

13. Whitsett JA, Wert SE, Weaver TE. Alveolar surfactant homeostasis and the pathogenesis of pulmonary disease. Annu Rev Med. 2010; 61:105–119. [PubMed: 19824815]

14. Seaton BA, Crouch EC, McCormack FX, Head JF, Hartshorn KL, Mendelsohn R. Structural determinants of pattern recognition by lung collectins. Innate Immun. 2010; 16:143–150. (Review). [PubMed: 20423923]

15. Balamayooran T, Balamayooran G, Jeyaseelan S. Toll-like receptors and NOD-like receptors in pulmonary antibacterial immunity. Innate Immun. 2010; 16:201–210. (Review). [PubMed: 20418253]

16. Opitz B, van LV, Eitel J, Suttorp N. Innate immune recognition in infectious and noninfectious diseases of the lung. Am J Respir Crit Care Med. 2010; 181:1294–1309. [PubMed: 20167850]

17. Hippenstiel S, Opitz B, Schmeck B, Suttorp N. Lung epithelium as a sentinel and effector system in pneumonia — molecular mechanisms of pathogen recognition and signal transduction. Respir Res. 2006; 7:97. [PubMed: 16827942]

18. Shimizu T, Kida Y, Kuwano K. A dipalmitoylated lipoprotein from *Mycoplasma pneumoniae* activates NF-kappa B through TLR1, TLR2, and TLR6. J Immunol. 2005; 175:4641–4646. [PubMed: 16177110]

19. Cao F, Castrillo A, Tontonoz P, Re F, Byrne GI. *Chlamydia pneumoniae* — induced macrophage foam cell formation is mediated by Toll-like receptor 2. Infect Immun. 2007; 75:753–759. [PubMed: 17145941]

20. Munoz N, Van ML, Marques JM, Rial A, Sirard JC, Chabalgoity JA. Mucosal administration of flagellin protects mice from *Streptococcus pneumoniae* lung infection. Infect Immun. 2010; 78:4226–4233. [PubMed: 20643849]

21. Vinzing M, Eitel J, Lippmann J, Hocke AC, Zahlten J, Slevogt H, N'guessan PD, Gunther S, Schmeck B, Hippenstiel S, et al. NAIP and Ipaf control *Legionella pneumophila* replication in human cells. J Immunol. 2008; 180:6808–6815. [PubMed: 18453601]

22. Davis KM, Nakamura S, Weiser JN. Nod2 sensing of lysozyme-digested peptidoglycan promotes macrophage recruitment and clearance of *S. pneumoniae* colonization in mice. J Clin Invest. 2011; 121:3666–3676. [PubMed: 21841315]

23. Shimada K, Crother TR, Karlin J, Chen S, Chiba N, Ramanujan VK, Vergnes L, Ojcius DM, Arditi M. Caspase-1 dependent IL-1beta secretion is critical for host defense in a mouse model of *Chlamydia pneumoniae* lung infection. PLoS ONE. 2011; 6:e21477. [PubMed: 21731762]

24. Roses RE, Xu S, Xu M, Koldovsky U, Koski G, Czerniecki BJ. Differential production of IL-23 and IL-12 by myeloid-derived dendritic cells in response to TLR agonists. J Immunol. 2008; 181:5120–5127. [PubMed: 18802116]

25. Happel KI, Zheng M, Young E, Quinton LJ, Lockhart E, Ramsay AJ, Shellito JE, Schurr JR, Bagby GJ, Nelson S, Kolls JK. Roles of Toll-like receptor 4 and IL-23 in IL-17 expression in response to *Klebsiella pneumoniae* infection. J Immunol. 2003; 170:4432–4436. (Cutting edge). [PubMed: 12707317]

26. Bhan U, Ballinger MN, Zeng X, Newstead MJ, Cornicelli MD, Standiford TJ. Cooperative interactions between TLR4 and TLR9 regulate interleukin 23 and 17 production in a murine model of Gram negative bacterial pneumonia. PLoS ONE. 2010; 5:e9896. [PubMed: 20360853]

27. 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] See annotation to Ref. [28••].

28. 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] This paper demonstrated that gammadelta T cells are crucial producers of IL-17 in the innate immune response in the lung and peritoneal cavity following infection with *M. tuberculosis* and *E. coli*, respectively.

29. 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]

30. Roark CL, Simonian PL, Fontenot AP, Born WK, O'Brien RL. gammadelta T cells: an important source of IL-17. Curr Opin Immunol. 2008; 20:353–357. [PubMed: 18439808]

31. Chen K, McAleer JP, Lin Y, Paterson DL, Zheng M, Alcorn JF, Weaver CT, Kolls JK. Th17 cells mediate clade-specific, serotype-independent mucosal immunity. Immunity. 2011; 35:997–1009. [PubMed: 22195749]

32. 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]

33. Rieder SA, Nagarkatti P, Nagarkatti M. CD1d-independent activation of invariant natural killer T cells by staphylococcal enterotoxin B through major histocompatibility complex class II/T cell receptor interaction results in acute lung injury. Infect Immun. 2011; 79:3141–3148. [PubMed: 21628519]

34. Paget C, Ivanov S, Fontaine J, Renneson J, Blanc F, Pichavant M, Dumoutier L, Ryffel B, Renauld JC, Gosset P, et al. Interleukin-22 is produced by invariant natural killer T lymphocytes during influenza A virus infection: potential role in protection against lung epithelial damages. J Biol Chem. 2012; 287:8816–8829. [PubMed: 22294696]

35. Takatori H, Kanno Y, Watford WT, Tato CM, Weiss G, Ivanov II, Littman DR, O'Shea JJ. Lymphoid tissue inducer-like cells are an innate source of IL-17 and IL-22. J Exp Med. 2009; 206:35–41. [PubMed: 19114665]

36. Ye P, Rodriguez FH, Kanaly S, Stocking KL, Schurr J, Schwarzenberger P, Oliver P, Huang W, Zhang P, Zhang J, 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] This paper demonstrated the importance of IL-17R signlaing in response to *K. pneumoniae* infection. The authors showed that IL-17R knockout mice had impaired neutrophil recruitment in response to *K. pneumoniae* infection and ulimately were unable to control the infection.

37. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, Reinhart TA, McAllister F, Edeal J, Gaus K, et al. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med. 2008; 14:275–281. [PubMed: 18264110]

38. McAllister F, Henry A, Kreindler JL, Dubin PJ, Ulrich L, Steele C, Finder JD, Pilewski JM, Carreno BM, Goldman SJ, 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]

39. Kuestner RE, Taft DW, Haran A, Brandt CS, Brender T, Lum K, Harder B, Okada S, Ostrander CD, Kreindler JL, et al. Identification of the IL-17 receptor related molecule IL-17RC as the receptor for IL-17F. J Immunol. 2007; 179:5462–5473. [PubMed: 17911633]

40. Hoegl S, Bachmann M, Scheiermann P, Goren I, Hofstetter C, Pfeilschifter J, Zwissler B, Muhl H. Protective properties of inhaled IL-22 in a model of ventilator-induced lung injury. Am J Respir Cell Mol Biol. 2010

41. Morens DM, Taubenberger JK, Fauci AS. The persistent legacy of the 1918 influenza virus. N Engl J Med. 2009; 361:225–229. [PubMed: 19564629]

42. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis. 2008; 198:962–970. [PubMed: 18710327] This paper demonstrated that secondary bacterial pneumonias caused the majority of deaths in the 1918 Spanish flu epidemic, furthering our knowledge of how viral and bacterial respiratory infections interact.

43. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. Nat Med. 2008; 14:558–564. [PubMed: 18438414]

44. Shahangian A, Chow EK, Tian X, Kang JR, Ghaffari A, Liu SY, Belperio JA, Cheng G, Deng JC. Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice. J Clin Invest. 2009; 119:1910–1920. [PubMed: 19487810]

45. Kudva A, Scheller EV, Robinson KM, Crowe CR, Choi SM, Slight SR, Khader SA, Dubin PJ, Enelow RI, Kolls JK, Alcorn JF. Influenza A inhibits Th17-mediated host defense against bacterial pneumonia in mice. J Immunol. 2010

46. Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. Annu Rev Immunol. 2007; 25:821–852. [PubMed: 17201677]
47. 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]
48. Oestreich KJ, Weinmann AS. Transcriptional mechanisms that regulate T helper 1 cell differentiation. Curr Opin Immunol. 2012; 24:191–195. [PubMed: 22240120]
49. Flynn JL, Chan J, Triebold KJ, Dalton DK, Stewart TA, Bloom BR. An essential role for interferon gamma in resistance to *Mycobacterium tuberculosis* infection. J Exp Med. 1993; 178:2249–2254. [PubMed: 7504064] See annotation to Ref. [50•].
50. Cooper AM, Dalton DK, Stewart TA, Griffin JP, Russell DG, Orme IM. Disseminated tuberculosis in interferon gamma gene-disrupted mice. J Exp Med. 1993; 178:2243–2247. [PubMed: 8245795] By using IFN-gamma knockout mice, this paper demonstrated that IFN-gamma plays an essential role in immunity against intracellular pathogens, such as *M. tuberculosis*.
51. Harding CV, Boom WH. Regulation of antigen presentation by *Mycobacterium tuberculosis*: a role for Toll-like receptors. Nat Rev Microbiol. 2010; 8:296–307. [PubMed: 20234378]
52. Gattoni A, Parlato A, Vangieri B, Bresciani M, Derna R. Interferon-gamma: biologic functions and HCV therapy (type I/II) (1 of 2 parts). Clin Ter. 2006; 157:377–386. [PubMed: 17051976]
53. Tudhope SJ, Catley MC, Fenwick PS, Russell RE, Rumsey WL, Newton R, Barnes PJ, Donnelly LE. The role of IkappaB kinase 2, but not activation of NF-kappaB, in the release of CXCR3 ligands from IFN-gamma-stimulated human bronchial epithelial cells. J Immunol. 2007; 179:6237–6245. [PubMed: 17947699]
54. 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]
55. Doffinger R, Dupuis S, Picard C, Fieschi C, Feinberg J, Barcenas-Morales G, Casanova JL. Inherited disorders of IL-12- and IFNgamma-mediated immunity: a molecular genetics update. Mol Immunol. 2002; 38:903–909. [PubMed: 12009568]
56. Atherton HC, Jones G, Danahay H. IL-13-induced changes in the goblet cell density of human bronchial epithelial cell cultures: MAP kinase and phosphatidylinositol 3-kinase regulation. Am J Physiol Lung Cell Mol Physiol. 2003; 285:L730–L739. [PubMed: 12794003]
57. Oliphant CJ, Barlow JL, McKenzie AN. Insights into the initiation of type 2 immune responses. Immunology. 2011; 134:378–385. [PubMed: 22044021]
58. Malley R, Anderson PW. Serotype-independent pneumococcal experimental vaccines that induce cellular as well as humoral immunity. Proc Natl Acad Sci U S A. 2012; 109:3623–3627. [PubMed: 22308483] This paper demonstrates that vaccination with killed, noncapsulated *S. pneumoniae* can lead to increased immunity against other pneumococcal serotypes through stimulation of IL-17A and production of plasma antibodies, a finding which has also been demonstrated in a *K. pneumoniae* model (see Ref. [31]).
59. Anderson EL, Kennedy DJ, Geldmacher KM, Donnelly J, Mendelman PM. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. J Pediatr. 1996; 128:649–653. [PubMed: 8627437]
60. Wiertsema SP, Baynam G, Khoo SK, Veenhoven RH, van HN, Zhang G, Laing IA, Rijkers GT, Goldblatt J, Sanders EA, Le Souef PN. Impact of genetic variants in IL-4, IL-4 RA and IL-13 on the anti-pneumococcal antibody response. Vaccine. 2007; 25:306–313. [PubMed: 16914241]
61. Khader SA, Gaffen SL, Kolls JK. Th17 cells at the crossroads of innate and adaptive immunity against infectious diseases at the mucosa. Mucosal Immunol. 2009; 2:403–411. [PubMed: 19587639]
62. Infante-Duarte C, Horton HF, Byrne MC, Kamradt T. Microbial lipopeptides induce the production of IL-17 in Th cells. J Immunol. 2000; 165:6107–6115. [PubMed: 11086043]
63. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, Weaver CT. 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] See annotation to Ref. [64•].

64. Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, Wang Y, Hood L, Zhu Z, Tian Q, Dong C. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol. 2005; 6:1133–1141. [PubMed: 16200068] This paper demonstrated that Th17 cells arose from a distinct lineage and not from Th1 or Th2 cells. The authors of these papers demonstrated that precursor cells could differentiate into Th17 cells in the absence of IFN-gamma and IL-4 and independently of trascription factors STAT1 and STAT4.

65. Mathur AN, Chang HC, Zisoulis DG, Stritesky GL, Yu Q, O'Malley JT, Kapur R, Levy DE, Kansas GS, Kaplan MH. Stat3 and Stat4 direct development of IL-17-secreting Th cells. J Immunol. 2007; 178:4901–4907. [PubMed: 17404271]

66. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, Kanno Y, Spalding C, Elloumi HZ, Paulson ML, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature. 2008; 452:773–776. [PubMed: 18337720] This clinical study demonstrated that humans with hyper-IgE syndrome had the inability to mount a normal Th17 response due to mutations in STAT3, thus explaining the recurrent pulmonary infections seen in these patients.

67. de BL, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M, Feinberg J, von BH, Samarina A, Janniere L, et al. Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. J Exp Med. 2008; 205:1543–1550. [PubMed: 18591412]

68. Minegishi Y, Saito M, Nagasawa M, Takada H, Hara T, Tsuchiya S, Agematsu K, Yamada M, Kawamura N, Ariga T, et al. Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome. J Exp Med. 2009; 206:1291–1301. [PubMed: 19487419]

69. Garty BZ, Ben-Baruch A, Rolinsky A, Woellner C, Grimbacher B, Marcus N. *Pneumocystis jirovecii* pneumonia in a baby with hyper-IgE syndrome. Eur J Pediatr. 2010; 169:35–37. [PubMed: 19308447]

70. Freeman AF, Davis J, Anderson VL, Barson W, Darnell DN, Puck JM, Holland SM. *Pneumocystis jiroveci* infection in patients with hyper-immunoglobulin E syndrome. Pediatrics. 2006; 118:e1271–e1275. [PubMed: 16940164]

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

72. Salzer U, Unger S, Warnatz K. Common variable immunodeficiency (CVID): exploring the multiple dimensions of a heterogeneous disease. Ann N Y Acad Sci. 2012; 1250:41–49. [PubMed: 22300655]

73. Kato A, Truong-Tran AQ, Scott AL, Matsumoto K, Schleimer RP. Airway epithelial cells produce B cell-activating factor of TNF family by an IFN-beta-dependent mechanism. J Immunol. 2006; 177:7164–7172. [PubMed: 17082634]

74. Loman S, Radl J, Jansen HM, Out TA, Lutter R. Vectorial transcytosis of dimeric IgA by the Calu-3 human lung epithelial cell line: upregulation by IFN-gamma. Am J Physiol. 1997; 272:L951–L958. [PubMed: 9176261]

75. Jaffar Z, Ferrini ME, Herritt LA, Roberts K. Lung mucosal Th17-mediated responses induce polymeric Ig receptor expression by the airway epithelium and elevate secretory IgA levels. J Immunol. 2009; 182:4507–4511. (Cutting edge). [PubMed: 19342622]

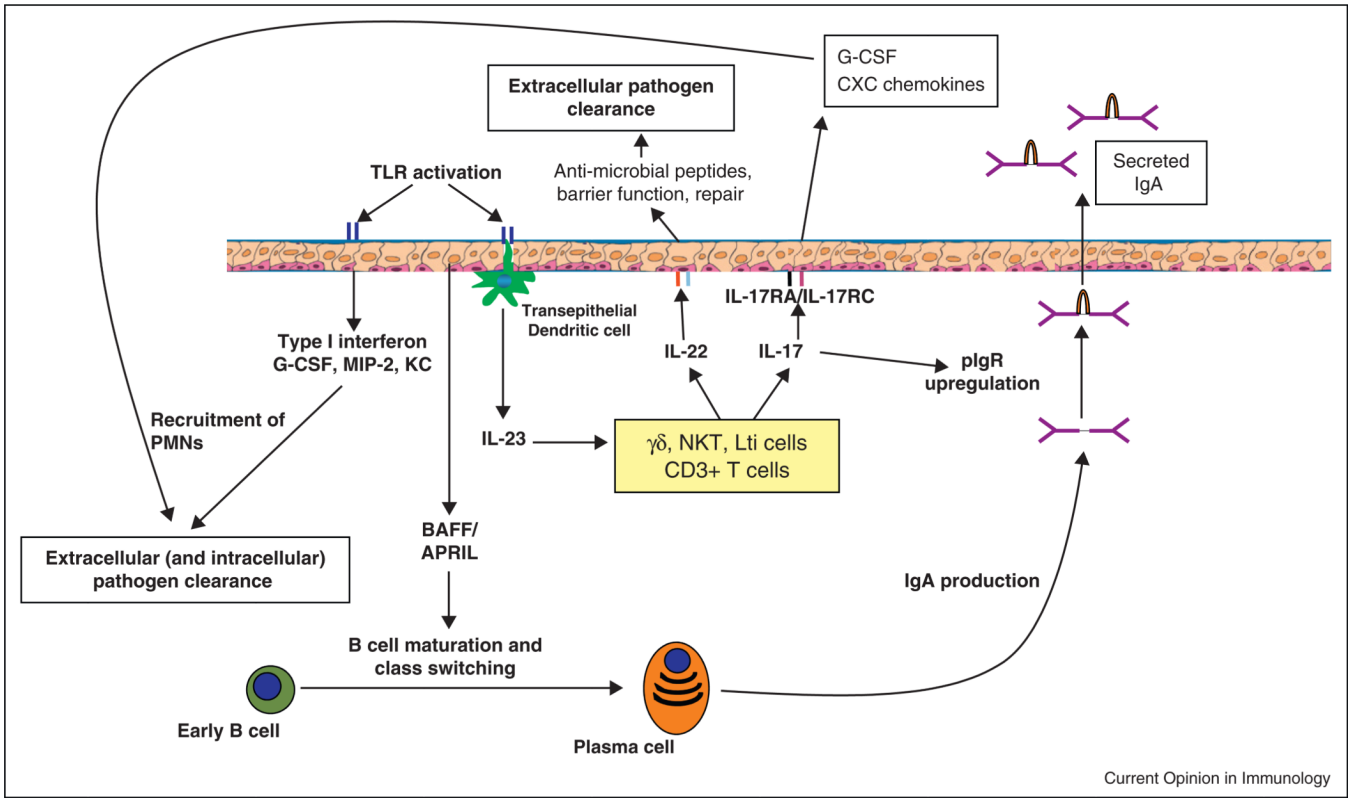

Figure 1.

The emerging role of lung epithelia in immunity. Lung epithelia and transepithelial dendritic cells can respond to invading bacteria using TLRs. After TLR activation, the lung epithelia release type I interferons, G-CSF, MIP-2, and KC which recruit polymorphonuclear cells, leading to enhanced pathogen clearance. Transepithelial dendritic cells release IL-23, which stimulates innate producers of IL-17 and IL-22. Lung epithelia, which express IL-17RA, IL-17RC, and IL-22R, responds by augmenting the expression of antimicrobial peptides, increasing barrier function, and releasing G-CSF. In addition, lung epithelial cells release BAFF and APRIL, proteins that promotes B cell maturation and class switching to IgA. Following IgA production, IL-17 can upregulate pIgR, leading to greater transcytosis of IgA into the lung lumen.

Table 1

TLRs and NLRs implicated in innate immunity in the lung in response to common causes of bacterial pneumonia (as reviewed in Refs [15,16,18,19,23])

Bacteria	TLRs	NLRs
Streptococcus pneumoniae	TLR2, 4, 9	NOD2
Klebsiella pneumoniae	TLR4, 9	NLRP3
Legionella pneumophila	TLR2, 4, 5, 9	NOD1, IPAF
Chlamydia pneumoniae	TLR2, 4	NOD1, 2, NLRP3
Mycoplasma pneumoniae	TLR1, 2, 6	–
Staphylococcus aureus	TLR2	NLRP3
Pseudomonas aeruginosa	TLR2, 4	NOD1, IPAF