Published in final edited form as:

Cytokine. 2009 ; 48(1-2): 156–160. doi:10.1016/j.cyto.2009.07.005.

Th17 cytokines and host-pathogen interactions at the mucosa:

dichotomies of help and harm

Janet Z. Liu^{1,2}, Milad Pezeshki^{1,2}, and Manuela Raffatellu^{1,2,*}

¹Department of Microbiology and Molecular Genetics, University of California Irvine, Irvine, California

²Institute for Immunology, University of California Irvine, Irvine, California

Abstract

The mucosal surfaces are often the first site of interaction between pathogenic microorganisms and the host. Activation of the mucosal immune response has the important function of containing an infection and preventing dissemination of pathogens to systemic sites (barrier function). Numerous lines of evidence suggest that the barrier function is orchestrated by a subset of cytokines (interleukin (IL)-17 and IL-22), which belong to the Th17 family. IL-17 and IL-22 induce expression of antimicrobial peptides and neutrophil chemoattractants at mucosal sites, and thus play an important role in controlling mucosal infections. However, there is increasing evidence that mucosal pathogens achieve greater colonization during inflammation because they are resistant to a subset of these antimicrobial responses. In this review we compare the antimicrobial responses elicited by Th17 cytokines during mucosal infections with four different pathogens: *Klebsiella pneumoniae*, *Citrobacter rodentium*, *Candida albicans* and *Salmonella typhimurium*. We will then discuss which responses may constitute the mucosal barrier, thus providing a benefit to the host, and which ones may promote the colonization of pathogens, thereby providing a benefit to the microbes.

1. Mucosal surfaces: a first line of defense

Mucosal surfaces are often the first interface between the host, the resident microbiota, and pathogenic microorganisms. In normal individuals, the mucosa constitutes a barrier against the systemic spread of microorganisms. Both the microbiota and pathogens are normally confined to mucosal sites by the local innate immune responses. However, in certain individuals the mucosal defenses are altered and thus commensals or pathogens may spread systemically. For instance, patients infected with the human immunodeficiency virus (HIV) clinically present with high concentrations of lipopolysaccharide (LPS) in the blood, indicating that Gram negative commensals may enter the blood stream from the gut [1]. Also, HIV-infected patients are more susceptible to bacteremia [2]. Elderly patients are also at high risk for bacteremia, mostly originating from the urinary tract, intra-abdominal sites and the lungs [3]. While it is accepted that these groups of patients have altered mucosal immunity, the precise defects have yet to be elucidated.

© 2009 Elsevier Ltd. All rights reserved.

*Correspondence, Manuela Raffatellu, MD, Department of Microbiology and Molecular Genetics, University of California, Irvine, Irvine, CA 92617, manuelar@uci.edu Fax: 949-824-8598 Tel: 949-824-0359

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

2. Th17 cytokines orchestrate early mucosal responses to mucosal pathogens

When pathogens approach the mucosal surface, the mucosal epithelium constitutes both a physical barrier and a first line of defense via mechanisms of innate immunity. To counter these impediments, pathogens can employ a repertoire of virulence factors that include enabling penetration through thick mucous layers (flagella), surface adherence (fimbriae and other adhesins) and induction of a host inflammatory response.

Direct interaction of microbes with epithelial cells and resident macrophages induces a stereotypic host response. Conserved structures (pathogen associated molecular patterns, PAMPs) are recognized by pattern recognition receptors (Toll-like receptors and Nod-like receptors) of epithelial cells and antigen presenting cells [4,5]. These cells are then activated and secrete chemokines and cytokines. For a long time, major research efforts have been directed towards investigating the direct interaction of pathogens with epithelial cells and antigen-presenting cells, which was considered sufficient for mounting an effective mucosal response. However, there is increasing evidence that several subsets of T cells are activated in the mucosa in response to pathogens [6].

Clinical evidence for the role of T cells as “gate keepers” in the mucosa comes from patients infected with HIV, wherein CD4⁺ T cells are severely depleted by the virus over time [7,8]. Importantly, while the number of CD4⁺ T cells in the blood is reduced quite slowly, the kinetics of CD4⁺ T cell depletion at mucosal sites (particularly in the gut) are much faster, with severe depletion occurring within the first few weeks following HIV infection [7,8]. This drop in mucosal CD4⁺ T cells correlates with increased susceptibility to mucosal infections. Notably, HIV-infected patients are more susceptible to bacteremia caused by intestinal pathogens like non-typhoidal *Salmonella*, and less commonly *Shigella* and *Campylobacter* [9-11]. From these epidemiological observations, it follows that T cells in the mucosa may be essential components of mucosal responses to pathogens.

A pioneering study on the role of T cells in the mucosal barrier was published in 1994 by Gautreaux and his colleagues, who showed that depletion of either the CD4⁺ or CD8⁺ T cell subsets resulted in increased translocation of non-pathogenic *E. coli* to the mesenteric lymph nodes [12]. Also, depletion of CD4⁺ and CD8⁺ T cells resulted in increased systemic dissemination of *S. typhimurium* to the spleen and liver [12]. Adoptive transfer of CD4⁺ and/or CD8⁺ T cells in mice previously depleted of T cells inhibited the translocation of *E. coli* from the GI tract [13]. Several other studies point towards a role of T cells in orchestrating mucosal responses to infections. In particular, a new subset of T cells, termed Th17 cells, has been recognized as a key component of mucosal immunity (reviewed in [14]).

Th17 cells are a distinct lineage from Th1 and Th2 cells [15], characterized by the release of a subset of cytokines: interleukin (IL-) 17A and IL-17F, IL-22 and IL-26 [16,17]. Receptors for IL-17A and IL-17F (IL-17Ra and IL-17Rc) are present in several cell types, including antigen presenting cells and epithelial cells [18,19]. In contrast, receptors for IL-22 and IL-26 appear to be localized to the epithelium [19-21]. Very little is known about the role of IL-26 during mucosal infection because rodents do not express this cytokine. For IL-17A/F and IL-22, expression increases at mucosal sites after infection with a number of pathogens including lung infection with *Klebsiella pneumoniae* [22,23], intestinal infections with *Citrobacter rodentium* [24-26] or *Salmonella typhimurium* [27,28], and colonization of the oral cavity with *Candida albicans* [29]. In each of these examples IL-17 and/or IL-22 are induced and contribute to localizing the infection to the mucosa, thus impeding dissemination of these pathogens beyond the initial site of infection.

K. pneumoniae infection of IL-17Ra^{-/-} mice results in increased death and systemic dissemination from the lung [22]. Moreover, *K. pneumoniae* infection is worsened if IL-22 is depleted from IL-17Ra^{-/-} mice [23]. Th17 cells are also activated during colonic infection to *C. rodentium* [24-26]. All the known mouse Th17 cytokines (IL-17A and IL-17F, IL-22) appear to play a role in controlling *C. rodentium* infection and the severity of gut pathology [24-26]. IL-17 but not IL-22 seems to be important for controlling *C. albicans* infection of the oral mucosa [29]. *S. typhimurium* infection induces expression of IL-17 and IL-22 in the intestinal mucosa of mice, calves and rhesus macaques [27,28]. In rhesus macaques, infection with the Simian Immunodeficiency Virus (SIV) causes depletion of Th17 cells, resulting in increased dissemination of *S. typhimurium* to the mesenteric lymph nodes [28]. This can be recapitulated in IL-17Ra^{-/-} mice, which have an increased bacterial load of *S. typhimurium* in the mesenteric lymph nodes and spleen [28].

Considering that IL-17 and IL-22 appear to play a role in orchestrating the mucosal barrier against different pathogens, it is not surprising that there is substantial overlap between expression of some known Th17-induced genes in response to various infectious agents, as shown in Table 1. It thus appears that early Th17 activation constitutes a stereotypic host response to mucosal infections.

3. IL-17 and IL-22 induce responses that control systemic dissemination of mucosal pathogens

The cytokines IL-17 and IL-22 orchestrate the mucosal response by inducing expression of several chemokines and antimicrobial peptides (Table 1). IL-17 and IL-22 stimulation of lung and gut epithelial cells induces expression of several antimicrobial responses and chemokines, including some CXC chemokines that are neutrophil chemoattractants [23,30-36]. Thus, neutrophil influx in the mucosa is at least partly dependent on IL-17 and IL-22. Moreover, both IL-17 and IL-22 stimulate granulopoiesis by inducing expression of G-CSF [22,23,35,37,38]. Neutrophils are an important first line of mucosal defense against bacterial infections. A low neutrophil count (neutropenia) is an important risk factor for bacteremia. One of the most common treatments for neutropenia is the administration of G-CSF, which is also employed in HIV patients [39,40]. In animal models, Th17 deficiency results in a decrease in neutrophil recruitment during lung infection with *K. pneumoniae*, gut infection with *S. typhimurium*, and oral infection with *C. albicans* [22,23,28,29]. Given that these pathogens are susceptible to neutrophil killing, it is likely that a defect in neutrophil recruitment may explain why these infections are less well controlled in the absence of Th17 responses.

Several antimicrobial responses are induced by IL-17 and IL-22 in the mucosa. Expression of secreted C-type lectins of the RegIII family is dependent on IL-22 [26]. IL-22 deficient mice infected with *C. rodentium* show increased mortality when compared to wild-type mice [26]. Nevertheless, administration of just Reg3γ to IL-22^{-/-} mice is sufficient to control infection with *C. rodentium* to a similar level as wild-type mice [26]. Induction of Reg3γ is also important to limit growth of vancomycin-resistant enterococci in the gut [41]. During *S. typhimurium* infection the expression of Reg3γ is dependent on IL-23, a cytokine upstream of IL-17 and IL-22 [42]. Reg3γ is not an effective antimicrobial against *S. typhimurium* in vitro, making it highly unlikely that it plays a role in controlling *S. typhimurium* bacterial numbers in vivo [43].

β-defensins are a major family of antimicrobial peptides present in mammals [44]. Expression of β-defensins is induced by Th17 cytokines in some infection models. For instance, induction of the antimicrobial peptide β-defensin 3 in response to infection with *C. albicans* is dependent on IL-17 [29]. β-defensin 3 has candidacidal activity in vitro [29,45] and saliva from wild-type mice, but not IL-17Ra^{-/-} mice, has candidacidal activity, indicating that IL-17 also controls *C.*

albicans proliferation by promoting secretion of antimicrobial peptides [29]. Several β -defensins are induced in the gut in response to *C. rodentium* infections, with induction of β -defensin 1, 3, 4 dependent on IL-17 and IL-17F [25].

As different subsets of Th17-mediated responses appear to control infection with different mucosal pathogens, further work is needed to investigate which aspects of the Th17 response are effective in controlling specific pathogens.

4. IL-17 and IL-22 induce antimicrobial responses that facilitate growth of mucosal pathogens

There are many studies indicating that Th17-induced responses are beneficial to the host as they provide containment of infections to the mucosa. In spite of this, pathogens colonize mucosal surfaces during inflammation quite successfully. There is increasing evidence that inflammation can be beneficial to a pathogen and promote its colonization and host-to-host transmission. The case of the gut is emblematic as this mucosal surface is colonized by a barrier of millions of protective bacteria (the resident microbiota) that is severely compromised upon initiation of inflammation [46].

Colonic infection with *C. rodentium* results in changes of microbial composition, with preferential elimination of a subset of microbiota and overgrowth of *C. rodentium* itself and other gamma-Proteobacteria [47]. It is thus highly likely that a subset of antimicrobial responses induced by *C. rodentium* in the gut alters the composition of the microbiota and promotes *C. rodentium* gut colonization during inflammation. In a similar fashion, infection with *S. typhimurium* results in alteration of the gut microbiota composition, with growth suppression of *Bacteriodes* spp. and *Firmicutes* spp. [48,49]. This results in a higher degree of *S. typhimurium* colonization of the inflamed gut. The observation that avirulent *S. typhimurium* mutants which fail to trigger gut inflammation are outcompeted by the resident microbiota indicates that both microbiota suppression and the ability to thrive in the inflamed intestine benefit *S. typhimurium*. In line with the observation that inflammation is beneficial for pathogens is the observation that only *S. typhimurium* strains which trigger an inflammatory response are transmitted to the next susceptible host [50]. From these studies, it appears that intestinal pathogens exploit the mucosal host response to suppress growth of the resident microbiota and colonize the inflamed gut.

5. Evasion of mucosal responses is essential for colonization

One of the most important strategies for successful colonization is a pathogen's ability to access nutrients in the context of inflammation. Motility and chemotaxis are important to direct pathogens towards sources of nutrients like those provided by mucins [51] which are upregulated in vivo and in vitro by IL-17 and IL-22 stimulation [23,31,33]. Enteraggative *Escherichia coli* (EAEC), uropathogenic *E. coli* (UPEC) and *Shigella flexneri* secrete a serine protease autotransporter (Pic) which degrades mucin [52,53]. The Pic mucinase enhances EAEC colonization of the mouse gastrointestinal tract and growth in the presence of mucin, thereby constituting a virulence factor which enhances the fitness of a pathogen in the hostile gut environment [53].

Other essential nutrients for bacterial growth are metal ions including iron, zinc and manganese. Consequently, one host strategy to fight bacterial infection is to deprive bacteria of said ions. Iron is largely bound to serum transferrin and, in inflamed mucosal sites, to lactoferrin secreted by neutrophils [54]. To overcome these host defense mechanisms, bacteria secrete iron chelators with higher affinity than transferrin and lactoferrin, termed siderophores [55,56]. Once siderophores are bound to iron, they are internalized by specialized transport systems.

One of these siderophores, termed enterochelin, is a target of the host antimicrobial protein lipocalin-2 [57]. Enterochelin is produced by most members of the Enterobacteriaceae including *Citrobacter* spp., *E. coli* spp., *Klebsiella* spp., and *Salmonella* spp. [58-61]. Lipocalin-2 is an antimicrobial peptide secreted at high levels by epithelial cells at mucosal surfaces in response to IL-17 and IL-22 stimulation, thus mostly in response to infection [23, 29,31]. Lipocalin-2 binds to iron-laden enterochelin, effectively suppressing the growth of strains lacking other means of iron acquisition [57,62]. Some enteric pathogens (*Salmonella* spp, uropathogenic *E. coli*, and some strains of *Klebsiella*) produce additional siderophores and their receptors [63]. One of these siderophores, termed salmochelin, is a glycosylated form of enterochelin which is not bound by lipocalin 2 [64-67] and its expression renders pathogens resistant to lipocalin-2-mediated iron withholding [31,68-70]. Salmochelin-mediated resistance to lipocalin-2 promotes *S. typhimurium* colonization of the inflamed gut [31], but provides no benefit in the absence of gut inflammation or lipocalin-2 [31]. This indicates that iron acquisition during mucosal inflammation is an important virulence trait of pathogens trying to survive and proliferate in the inflamed gut.

In addition to salmochelin, other siderophores and their receptors may facilitate pathogen colonization. Some *K. pneumoniae* clinical isolates are susceptible to lipocalin-2 expressed in the lung [71]. However, *K. pneumoniae* expressing the siderophore yersiniabactins colonize the lung better than isogenic mutants impaired in yersiniabactin synthesis [72]. Some pathogenic *E. coli* produce the siderophores yersiniabactin and aerobactin in addition to salmochelin [73]. Acquisition of siderophores and additional iron uptake mechanisms may circumvent the inhibition of enterobactin mediated by lipocalin-2.

Lipocalin-2 expression is induced by several other mucosal pathogens. Both *Streptococcus pneumoniae* and *Haemophilus influenzae* induce expression of lipocalin-2 in the nasal mucosa [74]. In rhesus macaques, *Helicobacter pylori* infection induces expression of lipocalin-2 and other antimicrobials in the stomach [75]. Also *C. albicans* infection of the oral cavity in mice induces expression of lipocalin-2 [29]. All of these pathogens are not susceptible to lipocalin-2 antimicrobial activity, and the role of lipocalin-2 in these infection models has yet to be established. It is feasible that the expression of lipocalin-2 and other antimicrobial peptides promotes colonization of mucosal pathogens other than *S. typhimurium* by suppressing the growth of competitors.

Several other antimicrobial responses are induced in the mucosa in a Th17-dependent fashion. Expression of the S100A8 and S100A9 subunits of calprotectin - an antimicrobial peptide that chelates the essential nutrients zinc and manganese [76] - is also induced in response to IL-17 and IL-22 [17,26]. Inducible nitric oxide synthase (iNOS) expression also appears to be dependent on IL-22 and IFN- γ [36]. It will be important determine whether these antimicrobial responses play a role in mucosal immunity.

6. Conclusions

Recent studies reveal a role for Th17-mediated mucosal immunity in the early control of infection with a variety of organisms. The responses elicited by the cytokines IL-17 and IL-22 in the mucosa are important for controlling dissemination of infectious agents beyond the mucosa and constitute the mucosal barrier. These responses are thus beneficial to the host during an infection.

While some aspects of the Th17-mediated responses are beneficial to the host, others are exploited by mucosal pathogens to achieve greater colonization when competing for a niche with other microbes. This is a prime example of pathogens evolving to take advantage of key components of the immune response. Thus, Th17-mediated responses constitute a double-

edged sword: on one end, these responses are necessary to contain an infection to the mucosa, and on the other end they favor pathogen colonization (Figure 1). While a defect in Th17-mediated responses would likely impair mucosal colonization of pathogens, the reduced expression of antimicrobial peptides would also promote the dissemination of both pathogens and commensals from the mucosal surfaces. Sustained activation of Th17 cells is a hallmark of several autoimmune disorders, like multiple sclerosis, inflammatory bowel diseases, and psoriasis [78-80]. For this reason, blocking Th17 cell function is currently considered as a therapeutic option for many of these conditions. However, blockade of Th17 responses may also result in increased severity of mucosal infections and bacteremia, a side effect that requires careful evaluation.

Acknowledgments

The authors would like to thank Andreas Bäumlér and Sean-Paul Nuccio for helpful discussions. Work in MR laboratory is supported by Public Health Service Grant AI083619 and the IDSA ERF/NIFID Astellas Young Investigator Award.

References

- [1]. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte O, Altmann D, Blazar BR, Rodriguez B, Teixeira-Johnson L, Landay A, Martin JN, Hecht FM, Picker LJ, Lederman MM, Deeks SG, Douek DC. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* 2006;12:1365–71. [PubMed: 17115046]
- [2]. Bearman GM, Wenzel RP. Bacteremias: a leading cause of death. *Arch Med Res* 2005;36:646–59. [PubMed: 16216646]
- [3]. McBean M, Rajamani S. Increasing rates of hospitalization due to septicemia in the US elderly population, 1986-1997. *J Infect Dis* 2001;183:596–603. [PubMed: 11170985]
- [4]. Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. *Clin Microbiol Rev* 2009;22:240–73. Table of Contents. [PubMed: 19366914]
- [5]. Franchi L, Eigenbrod T, Munoz-Planillo R, Nunez G. The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis. *Nat Immunol* 2009;10:241–7. [PubMed: 19221555]
- [6]. van Wijk F, Cheroutre H. Intestinal T cells: facing the mucosal immune dilemma with synergy and diversity. *Semin Immunol* 2009;21:130–8. [PubMed: 19386513]
- [7]. Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, Nguyen PL, Khoruts A, Larson M, Haase AT, Douek DC. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med* 2004;200:749–59. [PubMed: 15365096]
- [8]. Guadalupe M, Reay E, Sankaran S, Prindiville T, Flamm J, McNeil A, Dandekar S. Severe CD4+ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. *J Virol* 2003;77:11708–17. [PubMed: 14557656]
- [9]. Glaser JB, Morton-Kute L, Berger SR, Weber J, Siegal FP, Lopez C, Robbins W, Landesman SH. Recurrent *Salmonella typhimurium* bacteremia associated with the acquired immunodeficiency syndrome. *Ann Intern Med* 1985;102:189–93. [PubMed: 3881073]
- [10]. Gordon MA. *Salmonella* infections in immunocompromised adults. *J Infect* 2008;56:413–22. [PubMed: 18474400]
- [11]. Tee W, Mijch A. *Campylobacter jejuni* bacteremia in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients: comparison of clinical features and review. *Clin Infect Dis* 1998;26:91–6. [PubMed: 9455515]
- [12]. Gautreaux MD, Deitch EA, Berg RD. T lymphocytes in host defense against bacterial translocation from the gastrointestinal tract. *Infect Immun* 1994;62:2874–84. [PubMed: 7911786]
- [13]. Gautreaux MD, Gelder FB, Deitch EA, Berg RD. Adoptive transfer of T lymphocytes to T-cell-depleted mice inhibits *Escherichia coli* translocation from the gastrointestinal tract. *Infect Immun* 1995;63:3827–34. [PubMed: 7558287]

- [14]. Dubin PJ, Kolls JK. Th17 cytokines and mucosal immunity. *Immunol Rev* 2008;226:160–71. [PubMed: 19161423]
- [15]. 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;6:1123–32. [PubMed: 16200070]
- [16]. Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, Basham B, Smith K, Chen T, Morel F, Lecron JC, Kastelein RA, Cua DJ, McClanahan TK, Bowman EP, de Waal Malefyt R. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol* 2007;8:950–7. [PubMed: 17676044]
- [17]. Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, Fouser LA. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J Exp Med* 2006;203:2271–9. [PubMed: 16982811]
- [18]. Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol*. 2009
- [19]. Xie MH, Aggarwal S, Ho WH, Foster J, Zhang Z, Stinson J, Wood WI, Goddard AD, Gurney AL. Interleukin (IL)-22, a novel human cytokine that signals through the interferon receptor-related proteins CRF2-4 and IL-22R. *J Biol Chem* 2000;275:31335–9. [PubMed: 10875937]
- [20]. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 increases the innate immunity of tissues. *Immunity* 2004;21:241–54. [PubMed: 15308104]
- [21]. Sheikh F, Baurin VV, Lewis-Antes A, Shah NK, Smirnov SV, Anantha S, Dickensheets H, Dumoutier L, Renauld JC, Zdanov A, Donnelly RP, Kotenko SV. Cutting edge: IL-26 signals through a novel receptor complex composed of IL-20 receptor 1 and IL-10 receptor 2. *J Immunol* 2004;172:2006–10. [PubMed: 14764663]
- [22]. Ye P, Rodriguez FH, Kanaly S, Stocking KL, Schurr J, Schwarzenberger P, Oliver P, Huang W, Zhang P, Zhang J, Shellito JE, Bagby GJ, Nelson S, Charrier K, Peschon JJ, Kolls JK. 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;194:519–27. [PubMed: 11514607]
- [23]. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, Reinhart TA, McAllister F, Edeal J, Gaus K, Husain S, Kreindler JL, Dubin PJ, Pilewski JM, Myerburg MM, Mason CA, Iwakura Y, Kolls JK. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. *Nat Med* 2008;14:275–81. [PubMed: 18264110]
- [24]. Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, Hatton RD, Wahl SM, Schoeb TR, Weaver CT. Transforming growth factor-beta induces development of the T(H) 17 lineage. *Nature* 2006;441:231–4. [PubMed: 16648837]
- [25]. Ishigame H, Kakuta S, Nagai T, Kadoki M, Nambu A, Komiyama Y, Fujikado N, Tanahashi Y, Akitsu A, Kotaki H, Sudo K, Nakae S, Sasakawa C, Iwakura Y. Differential roles of interleukin-17A and -17F in host defense against mucocutaneous bacterial infection and allergic responses. *Immunity* 2009;30:108–19. [PubMed: 19144317]
- [26]. Zheng Y, Valdez PA, Danilenko DM, Hu Y, Sa SM, Gong Q, Abbas AR, Modrusan Z, Ghilardi N, de Sauvage FJ, Ouyang W. Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. *Nat Med* 2008;14:282–9. [PubMed: 18264109]
- [27]. Raffatellu M, Chessa D, Wilson RP, Dusold R, Rubino S, Bauml A. The Vi capsular antigen of *Salmonella enterica* serotype Typhi reduces Toll-like receptor-dependent interleukin-8 expression in the intestinal mucosa. *Infect Immun* 2005;73:3367–74. [PubMed: 15908363]
- [28]. Raffatellu M, Santos RL, Verhoeven DE, George MD, Wilson RP, Winter SE, Godinez I, Sankaran S, Paixao TA, Gordon MA, Kolls JK, Dandekar S, Bauml A. Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes *Salmonella* dissemination from the gut. *Nat Med* 2008;14:421–8. [PubMed: 18376406]
- [29]. Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, Ho AW, Hai JH, Yu JJ, Jung JW, Filler SG, Masso-Welch P, Edgerton M, Gaffen SL. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. *J Exp Med* 2009;206:299–311. [PubMed: 19204111]

- [30]. Awane M, Andres PG, Li DJ, Reinecker HC. NF-kappa B-inducing kinase is a common mediator of IL-17-, TNF-alpha-, and IL-1 beta-induced chemokine promoter activation in intestinal epithelial cells. *J Immunol* 1999;162:5337–44. [PubMed: 10228009]
- [31]. Raffatellu M, George MD, Akiyama Y, Hornsby MJ, Nuccio SP, Paixao TA, Butler BP, Chu H, Santos RL, Berger T, Mak TW, Tsois RM, Bevins CL, Solnick JV, Dandekar S, Baumler AJ. Lipocalin-2 resistance confers an advantage to *Salmonella enterica* serotype Typhimurium for growth and survival in the inflamed intestine. *Cell Host Microbe* 2009;5:476–86. [PubMed: 19454351]
- [32]. Andoh A, Zhang Z, Inatomi O, Fujino S, Deguchi Y, Araki Y, Tsujikawa T, Kitoh K, Kim-Mitsuyama S, Takayanagi A, Shimizu N, Fujiyama Y. Interleukin-22, a member of the IL-10 subfamily, induces inflammatory responses in colonic subepithelial myofibroblasts. *Gastroenterology* 2005;129:969–84. [PubMed: 16143135]
- [33]. Chen Y, Thai P, Zhao YH, Ho YS, DeSouza MM, Wu R. Stimulation of airway mucin gene expression by interleukin (IL)-17 through IL-6 paracrine/autocrine loop. *J Biol Chem* 2003;278:17036–43. [PubMed: 12624114]
- [34]. Kao CY, Huang F, Chen Y, Thai P, Wachi S, Kim C, Tam L, Wu R. Up-regulation of CC chemokine ligand 20 expression in human airway epithelium by IL-17 through a JAK-independent but MEK/NF-kappaB-dependent signaling pathway. *J Immunol* 2005;175:6676–85. [PubMed: 16272323]
- [35]. McAllister F, Henry A, Kreindler JL, Dubin PJ, Ulrich L, Steele C, Finder JD, Pilewski JM, Carreno BM, Goldman SJ, Pirhonen J, Kolls JK. 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;175:404–12. [PubMed: 15972674]
- [36]. Ziesche E, Bachmann M, Kleinert H, Pfeilschifter J, Muhl H. The interleukin-22/STAT3 pathway potentiates expression of inducible nitric-oxide synthase in human colon carcinoma cells. *J Biol Chem* 2007;282:16006–15. [PubMed: 17438334]
- [37]. Cai XY, Gommoll CP Jr. Justice L, Narula SK, Fine JS. Regulation of granulocyte colony-stimulating factor gene expression by interleukin-17. *Immunol Lett* 1998;62:51–8. [PubMed: 9672148]
- [38]. Numasaki M, Takahashi H, Tomioka Y, Sasaki H. Regulatory roles of IL-17 and IL-17F in G-CSF production by lung microvascular endothelial cells stimulated with IL-1beta and/or TNF-alpha. *Immunol Lett* 2004;95:97–104. [PubMed: 15325804]
- [39]. Kuritzkes DR. Neutropenia, neutrophil dysfunction, and bacterial infection in patients with human immunodeficiency virus disease: the role of granulocyte colony-stimulating factor. *Clin Infect Dis* 2000;30:256–60. [PubMed: 10671324]
- [40]. Pitak DL. Neutrophil deficiency and dysfunction in HIV-infected patients. *Am J Health Syst Pharm* 1999;56(Suppl 5):S9–16. [PubMed: 10613381]
- [41]. Brandl K, Plitas G, Mihu CN, Ubeda C, Jia T, Fleisher M, Schnabl B, DeMatteo RP, Pamer EG. Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. *Nature* 2008;455:804–7. [PubMed: 18724361]
- [42]. Godinez I, Raffatellu M, Chu H, Paixao TA, Haneda T, Santos RL, Bevins CL, Tsois RM, Baumler AJ. Interleukin-23 orchestrates mucosal responses to *Salmonella enterica* serotype Typhimurium in the intestine. *Infect Immun* 2009;77:387–98. [PubMed: 18955477]
- [43]. Cash HL, Whitham CV, Behrendt CL, Hooper LV. Symbiotic bacteria direct expression of an intestinal bactericidal lectin. *Science* 2006;313:1126–30. [PubMed: 16931762]
- [44]. Diamond G, Bevins CL. beta-Defensins: endogenous antibiotics of the innate host defense response. *Clin Immunol Immunopathol* 1998;88:221–5. [PubMed: 9743607]
- [45]. Vylkova S, Li XS, Berner JC, Edgerton M. Distinct antifungal mechanisms: beta-defensins require *Candida albicans* Ssa1 protein, while Trk1p mediates activity of cysteine-free cationic peptides. *Antimicrob Agents Chemother* 2006;50:324–31. [PubMed: 16377704]
- [46]. Pedron T, Sansonetti P. Commensals, bacterial pathogens and intestinal inflammation: an intriguing menage a trois. *Cell Host Microbe* 2008;3:344–7. [PubMed: 18541210]

- [47]. Lupp C, Robertson ML, Wickham ME, Sekirov I, Champion OL, Gaynor EC, Finlay BB. Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae. *Cell Host Microbe* 2007;2:204. [PubMed: 18030708]
- [48]. Stecher B, Robbani R, Walker AW, Westendorf AM, Barthel M, Kremer M, Chaffron S, Macpherson AJ, Buer J, Parkhill J, Dougan G, von Mering C, Hardt WD. Salmonella enterica serovar typhimurium exploits inflammation to compete with the intestinal microbiota. *PLoS Biol* 2007;5:2177–89. [PubMed: 17760501]
- [49]. Barman M, Unold D, Shifley K, Amir E, Hung K, Bos N, Salzman N. Enteric salmonellosis disrupts the microbial ecology of the murine gastrointestinal tract. *Infect Immun* 2008;76:907–15. [PubMed: 18160481]
- [50]. Lawley TD, Bouley DM, Hoy YE, Gerke C, Relman DA, Monack DM. Host transmission of Salmonella enterica serovar Typhimurium is controlled by virulence factors and indigenous intestinal microbiota. *Infect Immun* 2008;76:403–16. [PubMed: 17967858]
- [51]. Stecher B, Barthel M, Schlumberger MC, Haberli L, Rabsch W, Kremer M, Hardt WD. Motility allows *S. Typhimurium* to benefit from the mucosal defence. *Cell Microbiol* 2008;10:1166–80. [PubMed: 18241212]
- [52]. Henderson IR, Czeizulin J, Eslava C, Noriega F, Nataro JP. Characterization of pic, a secreted protease of *Shigella flexneri* and enteroaggregative *Escherichia coli*. *Infect Immun* 1999;67:5587–96. [PubMed: 10531204]
- [53]. Harrington SM, Sheikh J, Henderson IR, Ruiz-Perez F, Cohen PS, Nataro JP. The Pic protease of enteroaggregative *Escherichia coli* promotes intestinal colonization and growth in the presence of mucin. *Infect Immun* 2009;77:2465–73. [PubMed: 19349428]
- [54]. Ong ST, Ho JZ, Ho B, Ding JL. Iron-withholding strategy in innate immunity. *Immunobiology* 2006;211:295–314. [PubMed: 16697921]
- [55]. Braun V, Hantke K, Koster W. Bacterial iron transport: mechanisms, genetics, and regulation. *Met Ions Biol Syst* 1998;35:67–145. [PubMed: 9444760]
- [56]. Ratledge C. Iron metabolism and infection. *Food Nutr Bull* 2007;28:S515–23. [PubMed: 18297890]
- [57]. Flo TH, Smith KD, Sato S, Rodriguez DJ, Holmes MA, Strong RK, Akira S, Aderem A. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestering iron. *Nature* 2004;432:917–21. [PubMed: 15531878]
- [58]. Khashe S, Janda JM. Iron utilization studies in *Citrobacter* species. *FEMS Microbiol Lett* 1996;137:141–6. [PubMed: 8998976]
- [59]. Braun V. Iron uptake by *Escherichia coli*. *Front Biosci* 2003;8:s1409–21. [PubMed: 12957834]
- [60]. Kingsley R, Rabsch W, Stephens P, Roberts M, Reissbrodt R, Williams PH. Iron supplying systems of *Salmonella* in diagnostics, epidemiology and infection. *FEMS Immunol Med Microbiol* 1995;11:257–64. [PubMed: 8541802]
- [61]. Podschun R, Fischer A, Ullmann U. Siderophore production of *Klebsiella* species isolated from different sources. *Zentralbl Bakteriol* 1992;276:481–6. [PubMed: 1535249]
- [62]. Berger T, Togawa A, Duncan GS, Elia AJ, You-Ten A, Wakeham A, Fong HE, Cheung CC, Mak TW. Lipocalin 2-deficient mice exhibit increased sensitivity to *Escherichia coli* infection but not to ischemia-reperfusion injury. *Proc Natl Acad Sci U S A* 2006;103:1834–9. [PubMed: 16446425]
- [63]. Crosa JH. Genetics and molecular biology of siderophore-mediated iron transport in bacteria. *Microbiol Rev* 1989;53:517–30. [PubMed: 2531838]
- [64]. Baumler AJ, Tsolis RM, van der Velden AW, Stojiljkovic I, Anic S, Heffron F. Identification of a new iron regulated locus of *Salmonella typhi*. *Gene* 1996;183:207–13. [PubMed: 8996108]
- [65]. Fischbach MA, Lin H, Zhou L, Yu Y, Abergel RJ, Liu DR, Raymond KN, Wanner BL, Strong RK, Walsh CT, Aderem A, Smith KD. The pathogen-associated *iroA* gene cluster mediates bacterial evasion of lipocalin 2. *Proc Natl Acad Sci U S A* 2006;103:16502–7. [PubMed: 17060628]
- [66]. Bister B, Bischoff D, Nicholson GJ, Valdebenito M, Schneider K, Winkelmann G, Hantke K, Sussmuth RD. The structure of salmochelins: C-glucosylated enterobactins of *Salmonella enterica*. *Biometals* 2004;17:471–81. [PubMed: 15259369]
- [67]. Hantke K, Nicholson G, Rabsch W, Winkelmann G. Salmochelins, siderophores of *Salmonella enterica* and uropathogenic *Escherichia coli* strains, are recognized by the outer membrane receptor IroN. *Proc Natl Acad Sci U S A* 2003;100:3677–82. [PubMed: 12655053]

- [68]. Fischbach MA, Lin H, Liu DR, Walsh CT. How pathogenic bacteria evade mammalian sabotage in the battle for iron. *Nat Chem Biol* 2006;2:132–8. [PubMed: 16485005]
- [69]. Crouch ML, Castor M, Karlinsey JE, Kalhorn T, Fang FC. Biosynthesis and IroC-dependent export of the siderophore salmochelin are essential for virulence of *Salmonella enterica* serovar Typhimurium. *Mol Microbiol* 2008;67:971–83. [PubMed: 18194158]
- [70]. Caza M, Lepine F, Milot S, Dozois CM. Specific roles of the *iroBCDEN* genes in virulence of an avian pathogenic *Escherichia coli* O78 strain and in production of salmochelins. *Infect Immun* 2008;76:3539–49. [PubMed: 18541653]
- [71]. Chan YR, Liu JS, Pociask DA, Zheng M, Mietzner TA, Berger T, Mak TW, Clifton MC, Strong RK, Ray P, Kolls JK. Lipocalin 2 is required for pulmonary host defense against *Klebsiella* infection. *J Immunol* 2009;182:4947–56. [PubMed: 19342674]
- [72]. Lawlor MS, O'Connor C, Miller VL. Yersiniabactin is a virulence factor for *Klebsiella pneumoniae* during pulmonary infection. *Infect Immun* 2007;75:1463–72. [PubMed: 17220312]
- [73]. Valdebenito M, Crumbliss AL, Winkelmann G, Hantke K. Environmental factors influence the production of enterobactin, salmochelin, aerobactin, and yersiniabactin in *Escherichia coli* strain Nissle 1917. *Int J Med Microbiol* 2006;296:513–20. [PubMed: 17008127]
- [74]. Nelson AL, Barasch JM, Bunte RM, Weiser JN. Bacterial colonization of nasal mucosa induces expression of siderocalin, an iron-sequestering component of innate immunity. *Cell Microbiol* 2005;7:1404–17. [PubMed: 16153241]
- [75]. Hornsby MJ, Huff JL, Kays RJ, Canfield DR, Bevins CL, Solnick JV. *Helicobacter pylori* induces an antimicrobial response in rhesus macaques in a *cag* pathogenicity island-dependent manner. *Gastroenterology* 2008;134:1049–57. [PubMed: 18395086]
- [76]. Corbin BD, Seeley EH, Raab A, Feldmann J, Miller MR, Torres VJ, Anderson KL, Dattilo BM, Dunman PM, Gerads R, Caprioli RM, Nacken W, Chazin WJ, Skaar EP. Metal chelation and inhibition of bacterial growth in tissue abscesses. *Science* 2008;319:962–5. [PubMed: 18276893]
- [77]. Abraham C, Cho JH. IL-23 and Autoimmunity: New Insights into the Pathogenesis of Inflammatory Bowel Disease. *Annu Rev Med*. 2008
- [78]. Louten J, Boniface K, de Waal Malefyt R. Development and function of TH17 cells in health and disease. *J Allergy Clin Immunol* 2009;123:1004–11. [PubMed: 19410689]
- [79]. Korn T. Pathophysiology of multiple sclerosis. *J Neurol* 2008;255(Suppl 6):2–6. [PubMed: 19300953]
- [80]. Fouser LA, Wright JF, Dunussi-Joannopoulos K, Collins M. Th17 cytokines and their emerging roles in inflammation and autoimmunity. *Immunol Rev* 2008;226:87–102. [PubMed: 19161418]

Figure 1. IL-17 and IL-22 orchestrate the mucosal barrier to pathogens

IL-17 and IL-22 are upregulated in the mucosa in response to several pathogens. These cytokines stimulate epithelial cells to produce CXC chemokines, with recruitment of neutrophils to the site of infections. Also, epithelial cells stimulated with IL-17 and IL-22 secrete antimicrobial peptides, including lipocalin-2, Reg3 γ and β -defensins. Some of the Th17-induced responses are beneficial to the host because they keep microorganisms localized to the mucosa, reducing pathogen dissemination. Some of the same subset of responses, however, are exploited by resistant microorganisms to colonize the inflamed mucosal surfaces. Thus, the Th17-induced responses constitute a double-edged sword for the host.

Table 1
Th17-mediated induction of chemokines and antimicrobial responses in different infection models

Chemokines/Antimicrobial peptides	<i>C. albicans</i>	<i>C. rodentium</i>	<i>K. pneumoniae</i>	<i>S. typhimurium</i>
CXCL-1			X [23]	X [28,31]
CXCL-5	X [29]		X [23]	X [28,31]
CXCL-2	X [29]			X [28,31]
CCL20	X [29]		X [23]	X [28,31]
S100A8	X [29]	X [26]		X [28,31]
S100A9	X [29]	X [26]		X [28,31]
Lipocalin-2	X [29]	X [25]	X [23]	X [28,31]
b-defensin 3	X [29]	X [25]		
Reg3g	X [29]	X [26]		X [42]
Reg3b	X [29]	X [26]		