HHS Public Access

Author manuscript

Curr Opin HIV AIDS. Author manuscript; available in PMC 2015 June 29.

Published in final edited form as:

Curr Opin HIV AIDS. 2010 March ; 5(2): 179–183. doi:10.1097/COH.0b013e328335ed3e.

Th17 cells and Job's syndrome: a model of skin bacterial translocation

Joshua D. Milner[1], **Netanya G. Sandler**[2], and **Daniel C. Douek**[2]

[1]Allergic Inflammation Unit, Laboratory of Allergic Diseases, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892

[2]Human Immunology Section, Vaccine Research Center, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892

Abstract

Purpose of review—Patients with HIES share with HIV patients a predisposition to infections, including candidiasis in autosomal dominant HIES (AD-HIES) and molluscum contagiousum in autosomal recessive HIES (AR-HIES). This review highlights the underlying pathogenesis of these diseases and their relevance to HIV infection.

Recent findings—Patients with mutations in *STAT3*, who lack Th17 cells, develop AD-HIES, while AR-HIES may be caused by mutations in *Tyk2* or *DOCK8*, associated with decreased expansion of CD8 T cells. Recent studies on patients with recurrent mucocutaneous candidiasis have led to the discovery of mutations in *CARD9* and *DECTIN-1*, genes key to the production of the Th17-driving cytokines IL-1β, IL-6, and IL-23. Studies of the peripheral blood of HIV+ patients have shown a decreased Th17:Th1 ratio, and Th17 cells were preferentially depleted from the gastrointestinal tract within weeks of SIV infection of rhesus macaques.

Summary—The consequences of inadequate Th17 production in primary immunodeficiency syndromes illustrate the role of Th17 cells in controlling pathogens to which HIV+ individuals are susceptible. Further understanding of the pathogenesis of opportunistic disease in HIV infection will likely require exploring the role of Th17 cells.

Keywords

Hyper IgE syndrome; Job's syndrome; Th17; STAT3; HIV

Introduction

Autosomal dominant Hyper IgE syndrome (HIES) was initially described in 1966 as Job's syndrome in several patients who had eosinophilia, eczema and recurrent infections of the

Correspondence: Daniel C. Douek, Vaccine Research Center, National Institutes of Health, 40 Convent Drive, Bethesda, MD 20892. Phone: 301-594-8484. ddouek@mail.nih.gov.

skin and pulmonary tract [1]. Six years later, markedly elevated serum IgE was measured in these patients, leading to the title of the Hyper IgE syndrome [2]. Further phenotypic descriptions of skeletal, vascular, dental, neurologic and connective tissue abnormalities solidified the syndrome as a unique multisystem disorder [3–6]. Recently, dominant negative mutations in the gene Signal Transduction and Activation of Transcription (STAT) 3 were identified to account for this syndrome [7–8], providing a unique opportunity to better understand the disease pathogenesis, and to learn more about the roles played by this multifunctional signal transducer and transcription factor. This review will highlight recent findings in the pathogenesis of HIES, its distinction from related disorders, and related studies in STAT3 and Th17 biology, paying specific attention to the mechanisms by which host defense could be compromised by mutations in STAT3.

HIES diagnosis

One of the critical difficulties in understanding AD HIES has been to differentiate it from the myriad of other diseases in which infection and high IgE could be found. The cardinal infectious features of HIES include recurrent cold staphylococcal abscesses, associated with an underlying dermatitis, staphylococcal pneumonia associated with lung cyst formation, oral candiadiasis and onychomycosis. Cardinal non-immunologic findings include joint hyperextensibility, recurrent minimal trauma fractures, and retained childhood dentition with high-arched palate. Of interest, despite high IgE, the rate of allergen-induced atopy such as specific food allergy, allergen-induced wheeze or allergic rhinitis, is not elevated in HIES. A scoring system was proposed which has been useful although not completely accurate, in diagnosing classical HIES [9].

The list of disorders of immunodeficiency associated with high IgE in addition to AD HIES includes Wiskott-Aldrich Syndrome, Omenn’s syndrome, atypical complete DiGeorge syndrome, Netherton’s syndrome, immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome [10] and a collection of disorders termed autosomal recessive Hyper-IgE Syndrome [11]. Within this last category, mutations in *TYK2* [12] and dedicator of cytokinesis 8 (*DOCK8*) [13*] have been described to cause the phenotype. Tyk2-deficient patients differ from typical HIES in that they lack most of the non-immunologic phenotypes and have pulmonary mycobacterial infections, a phenotype only seen in HIES patients with underlying structural lung defects [14]. Patients with DOCK8 deficiency, in contrast to HIES patients, have multiple specific allergies and a prominence of viral infections, especially of the skin, such as molluscum contagiousum, disseminated varicella, herpes zoster, and others, and they were found to have decreased expansion of activated CD8 T cells *in vitro*. Skin neoplastic disease is also seen in the DOCK8 deficient patients whereas lymphomas are the only neoplasms noted in HIES.

The spectrum of HIES and HIES-like diseases is broad and, as it becomes more readily diagnosed and recognized, may shed light on the individual pathways, not only the genes, which cause these diseases. Chatila et al reported a large series of cases of patients with infections and high IgE, coupled with a variety of non-immunologic phenotypes [15]. Of interest in their series, the phenotypes of patients with no STAT3 mutations were not significantly different from those who had STAT3 mutations. Furthermore, similar to

patients with AD HIES, the STAT3 mutant negative population showed a disruption of Th17 cell production, the key difference being that Th17 cells were inducible in patients with WT STAT3 despite being decreased in the periphery, whereas Th17 cells could not be induced in STAT3 mutant patients. This observation suggests that other abnormalities within the STAT3/TH17 axis might explain some of these diseases. A significant subset of these patients likely has DOCK8 mutations based on the viral infections with which they presented, while others whose clinical phenotypes appear strongly like typical AD-HIES did not have STAT3 mutations. It will be of significant interest to determine how many of these patients have mutations in regions of STAT3 that were not sequenced (such as non-coding regions) or other mutations in the STAT3 pathway, and how many have unrelated pathogeneses.

It also will be important to see the extent to which these pathways contribute to more common atopy. While one study did not detect STAT3 polymorphisms in a large cohort of atopic patients [16], it remains possible that the pathways highlighted by rare diseases of elevated IgE and infection may help better understand common allergic diseases.

HIES Pathogenesis

With the recent identification of dominant negative mutations in STAT3 in patients with AD-HIES, there have been a number of significant advances in understanding the pathophysiology of certain elements of the syndrome.

Markedly decreased Th17 generation has been a hallmark of patients with HIES [17*, 18, 19]. Recent descriptions of patients with recurrent mucocutaneous candidiasis and decreased Th17 production caused by mutations in *CARD9* [20*] and DECTIN1 [21*] has added to the evidence that Th17 cells play an important role in antifungal immunity. Coupled with data in mice deficient for the IL-17 receptor suggesting that this receptor is critical for control of oral candidiasis [22], a strong case can be made that the lack of Th17 cells predisposes HIES patients to fungal infections. IL-17 facilitates neutrophil proliferation and recruitment through induction of granulocyte colony stimulating factor (G-CSF) and IL-8 (CXCL8) in epithelial cells [23–26]. Neutrophils are critical for host defense against both *Candida* and *Staphylococcus*, killing the organisms by phagocytosis and reactive oxygen burst as well as by neutrophil extracellular traps [27–30]. Neutropenia and neutrophil dysfunction, as in chronic granulomatous disease, are well-recognized risk factors for invasive candidal and severe staphylococcal infections [30–32]. However, candidal and staphylococcal infections in HIES are limited to the skin and lung, suggesting that perhaps the neutrophils are functional but perhaps not trafficking to the site of infection. Indeed, numerous studies have demonstrated defective neutrophil chemotaxis in patients with HIES [33–34]. HIES T-cell supernatant was not able to induce CXCL8 production by human bronchial epithelial cells or keratinocytes but was able to induce its production by fibroplasts and HUVECs, suggesting that in HIES patients, the skin and lung may be preferentially unable to adequately recruit neutrophils in a timely manner [35]. In addition to neutrophils, β-defensins are important in host defense against Candida infections [22]. Mucosal surface β-defensin formation appears to be dependent upon production of IL-22, a Th17-associated cytokine that signals through STAT3 [36]. Indeed HIES T-cell supernatant is not able to induce β-defensins as compared

to wild-type. Furthermore, neutralization of IL-17 and IL-22 in normal T-cell supernatants abolishes their capacity to induce defensin expression in keratinocytes and bronchial epithelial cells [35].

However, not all of the disorders of mucocutaneous candidiasis described above and elsewhere [37] to be associated with marked reductions in Th17 cells are themselves associated with bacterial infections. Further complicating our understanding of the direct role of Th17 cells in host defense is the fact that as patients with HIES age, a significant proportion of them have few or no infections of any kind despite continuing to lack peripheral Th17 cells.

One possibility to explain the mucosal bacterial infections is that direct stimulation of defensin expression is impaired due to defective STAT3 signaling (presumably due to IL-22 stimulation) within the target tissues. Direct measurement of defensin expression in HIES will help answer this question. One recent piece of evidence which would suggest a direct role for IL-22 signaling in mucosal defensin production can be found in patients with IL-10 receptor mutations [38]. These patients have a congenital inflammatory bowel disease, likely due to impaired IL-10 signaling which has been shown in mouse models to lead to colitis due to the lack of anti-inflammatory properties of IL-10. One patient was found have a loss of function mutation in *IL-10RB*, which is significant since this receptor protein is also used by IL-22 for normal signaling. The presence of recurrent folliculitis and pneumonias reported in this patient argues for the critical role of IL-22 in preventing bacterial skin and lung infections, independent of the presence of TH17 cells. It is interesting that despite IL-10 also using STAT3 for signaling, HIES patients have no evidence of inflammatory bowel disease. This may be because STAT3 mutations are hypomorphic in HIES patients allowing for sufficient residual efficacy of IL-10 function, or the use of other STAT proteins by IL-10 in the absence of normal STAT3 function.

Another explanation for the infectious predilection in HIES has been defective antibody production. Indeed memory B-cells numbers are decreased in HIES [39], and antibody responses to vaccines can be variable [40]. However IVIG is not routinely used or needed in HIES, despite a number who are on it. One might have anticipated that T-follicular helper cell, CD4+ T-cells responsible for germinal center formation and normal B-cell help, might be impaired in HIES, given the dependence of TFH cells upon stat3 [41, 42] and bcl-6 [43–45] for TFH formation. However CXCR5+ cells are at normal frequencies in HIES [18], and recent data has shown that human T-cells can upregulate BCL-6 and other markers and functions of the T-follicular helper cells lineage in response to IL-12 via STAT4 [46, 47].

Similarities between HIES and HIV

The infections with which HIV-infected patients present overlap substantially with those of patients with HIES and HIES-like diseases. Persistent or recurrent mucocutaneous candidiasis is recognized as one of the most common opportunistic infections in HIV+ patients [48]. HIV infection increases the risk of *Staphylococcus aureus* bacteremia 17-fold [49]), and methicillin-resistant *Staphylococcus aureus* skin abscesses by 18-fold, with a high rate of recurrence [50, 51]. Furthermore, as in patients with *DOCK8* mutations, HIV-

infected patients are predisposed to severe herpes simplex, herpes zoster, human papillomavirus, and molluscum contagiosum infections [48]. In addition, some rare infections of HIES patients are seen in HIV patients, such as pneumonia caused by *Streptococcus* [52] or *Pneumocystis jiroveci* [53].

HIV-infected individuals have lower Th17:Th1 CD4 T cell ratios in the peripheral blood and preferential loss of Th17 cells from the gastrointestinal tract [54**]. Studies of SIV-infected rhesus macaques have revealed that the frequency of Th17 cells in healthy macaques is actually higher in the GI tract than in the periphery, and Th17 cells but not Th1 cells are depleted from the GI tract within the first several weeks of SIV infection. Furthermore, the frequency of Th17 cells in mucosal sites is inversely correlated with the SIV viral load [55**]. Cells from the terminal ileum of SIV-infected rhesus macaques fail to upregulate IL-17, IL-22, and IL-8 expression in response to *Salmonella typhimurium* infection and have higher bacterial loads in the mesenteric lymph nodes than SIV-uninfected macaques, suggesting that the infected monkeys have decreased local control of infection [56*]. Consistent with the finding of poor local control of bacteria is the presence of elevated LPS levels in the plasma of patients with HIV without active bacterial infections [57]. Th17 cells may also be essential for defense against both *Streptococcus pneumoniae* and *Pneumocystis jiroveci*, as administration of an anti-IL-17 neutralizing antibody leads to impairment of bacterial clearance in the former and increased fungal burden in the latter in mouse models [58, 59]. Treatment with antiretrovirals can restore CD4 T cells, including Th17 cells, in the GALT [60*], decrease LPS levels in the plasma [57], and decrease the frequency of opportunistic infections [48]. Thus, decreased peripheral Th17 cell frequencies or a decreased systemic Th17:Th1 ratio may predispose HIV-infected patients to certain infections, including some of the same pathogens to which HIES patients are susceptible.

Conclusion

Since Job’s syndrome was first described over 40 years ago, significant advances have been made in understanding the pathogenesis of this disease. Patients with HIV infection share immunologic and infectious manifestations of both AD HIES, caused by STAT3 mutations, and AR HIES associated with DOCK8 mutations and potentially inadequate CD8 T cell expansion. The Th17 deficiency seen in AD HIES likely predisposes these individuals to infections with *Candida* and *Staphylococcus* via impairment of neutrophil chemotaxis and defensin production. A similar phenomenon may explain the predilection for recurrent mucocutaneous candidiasis and staphylococcal infections, and other bacterial and fungal infections, in HIV-infected individuals. Similarly, HIES patients with DOCK8 mutations have inadequate control of usually latent viral infections, likely due to defects in CD8 T cell function. Given recent data demonstrating important roles for IL-21 [61–63], a cytokine that uses STAT3 for signaling, and blimp-1 [64–66], a STAT3 target, in CD8 memory functions, it is likely that continued study of both the STAT3 and DOCK8 mutations seen in HIES patients will shed more light on the mechanisms underlying both CD4 and CD8 T-cell memory functions in humans.

Acknowledgements

This work was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Allergy and Infectious Diseases.

References

1. Davis S, Schaller J, Wedgwood R. Job's Syndrome. Recurrent, "cold", staphylococcal abscesses. Lancet. 1966; 1:1013–1015. [PubMed: 4161105]
2. Buckley RH, Wray BB, Belmaker EZ. Extreme hyperimmunoglobulinemia E and undue susceptibility to infection. Pediatrics. 1972; 49:59–70. [PubMed: 5059313]
3. Ling JC, Freeman AF, Gharib AM, et al. Coronary artery aneurysms in patients with hyper IgE recurrent infection syndrome. Clin Immunol. 2007; 122:255–258. [PubMed: 17098478]
4. Grimbacher B, Holland SM, Gallin JI, et al. Hyper-IgE syndrome with recurrent infections--an autosomal dominant multisystem disorder. N Engl J Med. 1999; 340:692–702. [PubMed: 10053178]
5. Domingo DL, Freeman AF, Davis J, et al. Novel intraoral phenotypes in hyperimmunoglobulin-E syndrome. Oral Dis. 2008; 14:73–81. [PubMed: 18173452]
6. Freeman AF, Collura-Burke CJ, Patronas NJ, et al. Brain abnormalities in patients with hyperimmunoglobulin E syndrome. Pediatrics. 2007; 119:e1121–e1125. [PubMed: 17438082]
7. Minegishi Y, Saito M, Tsuchiya S, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature. 2007
8. Holland SMDF, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, Freeman AF, Demidowich A, Davis J, Turner ML, Anderson VL, Darnell DN, Welch PA, Kuhns DB, Frucht DM, Malech HL, Gallin JI, Kobayashi SD, Whitney AR, Voyich JM, Musser JM, Woellner C, Schäffer AA, Puck JM, Grimbacher B. STAT3 Mutations in the Hyper-IgE Syndrome. New England Journal of Medicine. 2007 epub ahead of print.
9. Grimbacher B, Schaffer AA, Holland SM, et al. Genetic linkage of hyper-IgE syndrome to chromosome 4. Am J Hum Genet. 1999; 65:735–744. [PubMed: 10441580]
10. Ozcan E, Notarangelo LD, Geha RS. Primary immune deficiencies with aberrant IgE production. J Allergy Clin Immunol. 2008; 122:1054–1062. quiz 1063-1054. [PubMed: 19084106]
11. Renner ED, Puck JM, Holland SM, et al. Autosomal recessive hyperimmunoglobulin E syndrome: a distinct disease entity. J Pediatr. 2004; 144:93–99. [PubMed: 14722525]
12. Minegishi Y, Saito M, Morio T, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity. 2006; 25:745–755. [PubMed: 17088085]
13. Zhang Q, Davis JC, Lamborn IT, et al. Combined Immunodeficiency Associated with DOCK8 Mutations. N Engl J Med. 2009 This article is the first to describe patients with DOCK8 mutations. They share similar susceptibilities to viral infections with HIV patients.
14. Melia E, Freeman AF, Shea YR, Hsu AP, Holland SM, Olivier KN. Pulmonary nontuberculous mycobacterial infections in hyper-IgE syndrome. J Allergy Clin Immunol. 2009; 124:617–618. [PubMed: 19733303]
15. Al Khatib S, Keles S, Garcia-Lloret M, et al. Defects along the T(H)17 differentiation pathway underlie genetically distinct forms of the hyper IgE syndrome. J Allergy Clin Immunol. 2009; 124:342–348. 348 e341–348 e345. [PubMed: 19577286]
16. Wjst M, Lichtner P, Meitinger T, Grimbacher B. STAT3 single-nucleotide polymorphisms and STAT3 mutations associated with hyper-IgE syndrome are not responsible for increased serum IgE serum levels in asthma families. Eur J Hum Genet. 2009; 17:352–356. [PubMed: 18841165]
17. Milner JD, Brenchley JM, Laurence A, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature. 2008; 452:773–776. [PubMed: 18337720] Patients with AD-HIES had previously been shown to have mutations in STAT3. The authors show that these patients fail to produce IL-17 in response to stimulation with *Candida albicans* and naïve cells from these patients will not differentiate into Th17 cells.

18. Ma CS, Chew GY, Simpson N, et al. Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. J Exp Med. 2008; 205:1551–1557. [PubMed: 18591410]
19. de Beaucoudrey L, Puel A, Filipe-Santos O, 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]
20. Glocker EO, Hennigs A, Nabavi M, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med. 2009; 361:1727–1735. [PubMed: 19864672] The authors describe a novel mutation in *CARD9*, which is essential for signaling of the antifungal pattern recognition receptor dectin-1, that confers susceptibility to mucocutaneous candidiasis. These patients have decreased Th17 cells, supporting the role for this population in defense against *Candida albicans*.
21. Ferwerda B, Ferwerda G, Plantinga TS, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med. 2009; 361:1760–1767. [PubMed: 19864674] Patients with a novel mutation in *DECTIN-1* are characterized. They were susceptible to recurrent candidiasis and had decreased production of IL-17 and TNF in response to stimulation with *Candida albicans*, adding further support to the need for IL-17 in protection against candidal infections.
22. Conti HR, Shen F, Nayyar N, et al. 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]
23. Fossiez F, Djossou O, Chomarat P, et al. T Cell Interleukin-17 Induces Stromal Cells to Produce Proinflammatory and Hematopoietic Cytokines. J. Exp. Med. 1996; 183:2411–2415. [PubMed: 8676060]
24. Jones C, 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]
25. Kawaguchi M, Kokubu F, Kuga H, et al. Modulation of bronchial epithelial cells by IL-17. J Allergy Clin Immunol. 2001; 108:804–809. [PubMed: 11692108]
26. Laan M, Cui Z, Hoshino H, et al. Neutrophil recruitment by human IL-17 via C-X-C chemokine release in the airways. J Immunol. 1999; 162:2347–2352. [PubMed: 9973514]
27. Lehrer R, Cline M. Interaction of Candida albicans with human leukocytes and serum. J Bacteriol. 1969; 98:996–1004. [PubMed: 4182532]
28. Nauseef W. How human neutrophils kill and degrade microbes: an integrated view. Immunol Rev. 2007; 219:88–102. [PubMed: 17850484]
29. Urban C, Ermert D, Schmid M, et al. Neutrophil extracellular traps contain calprotectin, a cytosolic protein complex involved in host defense against Candida albicans. PLoS Pathog. 2009; 5 Epub 2009 Oct 30.
30. Anwar S, Prince L, Foster S, et al. The rise and rise of Staphylococcus aureus: laughing in the face of granulocytes. Clin Exp Immunol. 2009; 157:216–224. [PubMed: 19604261]
31. Pappas P, Kauffman C, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009; 48:503–535. [PubMed: 19191635]
32. Antachopoulos C, Walsh T, Roilides E. Fungal infections in primary immunodeficiencies. Eur J Pediatr. 2007; 166:1099–1117. [PubMed: 17551753]
33. Hill H, Ochs H, Quie P, et al. Defect in neutrophil granulocyte chemotaxis in Job's syndrome of recurrent "cold" staphylococcal abscesses. Lancet. 1974; 2:617–619. [PubMed: 4137601]
34. Paslin D, Norman M. Atopic dermatitis and impaired neutrophil chemotaxis in Job's syndrome. Arch Dermatol. 1977; 113:801–805. [PubMed: 869552]
35. Minegishi Y, Saito M, Nagasawa M, 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]
36. Wolk K, Kunz S, Witte E, et al. IL-22 increases the innate immunity of tissues. Immunity. 2004; 21:241–254. [PubMed: 15308104]

37. Eyerich K, Foerster S, Rombold S, et al. Patients with chronic mucocutaneous candidiasis exhibit reduced production of Th17-associated cytokines IL-17 and IL-22. J Invest Dermatol. 2008; 128:2640–2645. [PubMed: 18615114]

38. Glocker EO, Kotlarz D, Boztug K, et al. Inflammatory Bowel Disease and Mutations Affecting the Interleukin-10 Receptor. N Engl J Med. 2009

39. Speckmann C, Enders A, Woellner C, et al. Reduced memory B cells in patients with hyper IgE syndrome. Clin Immunol. 2008; 129:448–454. [PubMed: 18835223]

40. Sheerin K, Buckley R. Antibody responses to protein, polysaccharide, and phi X174 antigens in the hyperimmunoglobulinemia E (hyper-IgE) syndrome. J Allergy Clin Immunol. 1991; 87:803–811. [PubMed: 1826506]

41. Eddahri F, Denanglaire S, Bureau F, et al. Interleukin-6/STAT3 signaling regulates the ability of naive T cells to acquire B-cell help capacities. Blood. 2009; 113:2426–2433. [PubMed: 19020307]

42. Nurieva RI, Chung Y, Hwang D, et al. Generation of T follicular helper cells is mediated by interleukin-21 but independent of T helper 1, 2, or 17 cell lineages. Immunity. 2008; 29:138–149. [PubMed: 18599325]

43. Johnston RJ, Poholek AC, DiToro D, et al. Bcl6 and Blimp-1 are reciprocal and antagonistic regulators of T follicular helper cell differentiation. Science. 2009; 325:1006–1010. [PubMed: 19608860]

44. Yu D, Rao S, Tsai LM, et al. The transcriptional repressor Bcl-6 directs T follicular helper cell lineage commitment. Immunity. 2009; 31:457–468. [PubMed: 19631565]

45. Nurieva RI, Chung Y, Martinez GJ, et al. Bcl6 mediates the development of T follicular helper cells. Science. 2009; 325:1001–1005. [PubMed: 19628815]

46. Schmitt N, Morita R, Bourdery L, et al. Human dendritic cells induce the differentiation of interleukin-21-producing T follicular helper-like cells through interleukin-12. Immunity. 2009; 31:158–169. [PubMed: 19592276]

47. Ma CS, Suryani S, Avery DT, et al. Early commitment of naive human CD4(+) T cells to the T follicular helper (T(FH)) cell lineage is induced by IL-12. Immunol Cell Biol. 2009; 87:590–600. [PubMed: 19721453]

48. Kaplan J, Benson C, Holmes K, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep. 2009; 58:1–207.

49. Laupland K, Ross T, Gregson D. Staphylococcus aureus bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000–2006. J Infect Dis. 2008; 198:336–343. [PubMed: 18522502]

50. Crum-Cianflone N, Burgi A, Hale B. Increasing rates of community-acquired methicillin-resistant Staphylococcus aureus infections among HIV-infected persons. Int J STD AIDS. 2007; 18:521–526. [PubMed: 17686212]

51. Crum-Cianflone N, Weekes J, Bavaro M. Recurrent community-associated methicillin-resistant Staphylococcus aureus infections among HIV-infected persons: incidence and risk factors. AIDS Patient Care STDS. 2009; 23:499–502. [PubMed: 19530952]

52. Donabedian H, Gallin J. The hyperimmunoglobulin E recurrent-infection (Job's) syndrome. A review of the NIH experience and the literature. Medicine. 1983; 62:195–208. [PubMed: 6348470]

53. Freeman A, Davis J, Anderson V, et al. Pneumocystis jiroveci infection in patients with hyper-immunoglobulin E syndrome. Pediatrics. 2006; 118:e1271–e1275. [PubMed: 16940164]

54. Brenchley J, Paiardini M, Knox K, et al. Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections. Blood. 2008; 112:2826–2835. [PubMed: 18664624] The authors describe a decrease in the ratio of Th17 to Th1 cells in the peripheral blood with a marked decrease in GI tract Th17 cells. These findings raise the possibility that many of the opportunistic infections develop because of a relative Th17 deficiency.

55. Cecchinato V, Trindade C, Laurence A, et al. Altered balance between Th17 and Th1 cells at mucosal sites predicts AIDS progression in simian immunodeficiency virus-infected macaques. Mucosal Immunol. 2008; 1:279–288. [PubMed: 19079189] Th17 cells are shown to be disproportionately located in the gastrointestinal tract and depleted within several weeks of

infection, with the percentage correlating inversely with viral load. Thus, the virus may drive Th17 depletion, or Th17 depletion may be related to the HIV enteropathy that contributes to disease progression.

56. Raffatellu M, Santos R, Verhoeven D, et al. Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes Salmonella dissemination from the gut. Nat Med. 2008; 14:421–428. [PubMed: 18376406] Depletion of Th17 cells contributes to the inability to control gastrointestinal organisms. This may, therefore, be a factor in microbial translocation observed in HIV and associated with systemic inflammation.
57. Brenchley J, Price D, Schacker T, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med. 2006; 12:1365–1371. [PubMed: 17115046]
58. Zhang Z, Clarke T, Weiser J. Cellular effectors mediating Th17-dependent clearance of pneumococcal colonization in mice. J Clin Invest. 2009; 119:1899–1909. [PubMed: 19509469]
59. Rudner X, Happel K, Young E, Shellito J. Interleukin-23 (IL-23)-IL-17 cytokine axis in murine Pneumocystis carinii infection. Infect Immun. 2007; 75:3055–3061. [PubMed: 17403873]
60. Macal M, Sankaran S, Chun T, et al. Effective CD4+ T-cell restoration in gut-associated lymphoid tissue of HIV-infected patients is associated with enhanced Th17 cells and polyfunctional HIV-specific T-cell responses. Mucosal Immunol. 2008; 1:475–488. [PubMed: 19079215] The Th17 deficiency that occurs in HIV infection can be at least partially reversed by antiretroviral therapy. Together with data supporting a role for Th17 cells in defending against opportunistic pathogens and potentially microbial translocation, these findings support additional benefits of antiretroviral therapy.
61. Elsaesser H, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection. Science. 2009; 324:1569–1572. [PubMed: 19423777]
62. Frohlich A, Kisielow J, Schmitz I, et al. IL-21R on T cells is critical for sustained functionality and control of chronic viral infection. Science. 2009; 324:1576–1580. [PubMed: 19478140]
63. Yi JS, Du M, Zajac AJ. A vital role for interleukin-21 in the control of a chronic viral infection. Science. 2009; 324:1572–1576. [PubMed: 19443735]
64. Kallies A, Xin A, Belz GT, Nutt SL. Blimp-1 transcription factor is required for the differentiation of effector CD8(+) T cells and memory responses. Immunity. 2009; 31:283–295. [PubMed: 19664942]
65. Rutishauser RL, Martins GA, Kalachikov S, et al. Transcriptional repressor Blimp-1 promotes CD8(+) T cell terminal differentiation and represses the acquisition of central memory T cell properties. Immunity. 2009; 31:296–308. [PubMed: 19664941]
66. Shin H, Blackburn SD, Intlekofer AM, et al. A role for the transcriptional repressor Blimp-1 in CD8(+) T cell exhaustion during chronic viral infection. Immunity. 2009; 31:309–320. [PubMed: 19664943]