Mucosal Immunol. 2008 Jul;1(4):279-88. Epub 2008 May 7.

Altered balance between Th17 and Th1 cells at mucosal sites predicts AIDS progression in simian immunodeficiency virus-infected macaques.

Cecchinato V, Trindade CJ, Laurence A, Heraud JM, Brenchley JM, Ferrari MG, Zaffiri L, Tryniszewska E, Tsai WP, Vaccari M, Parks RW, Venzon D, Douek DC, O'Shea JJ, Franchini G.

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Loss of CD4(+) T cells in the gut is necessary but not sufficient to cause AIDS in animal models, raising the possibility that a differential loss of CD4(+) T-cell subtypes may be important. We found that CD4(+) T cells that produce interleukin (IL)-17, a recently identified lineage of effector CD4(+) T-helper cells, are infected by SIV(mac251)in vitro and in vivo, and are found at lower frequency at mucosal and systemic sites within a few weeks from infection. In highly viremic animals, Th1 cells predominates over Th17 T cells and the frequency of Th17 cells at mucosal sites is negatively correlated with plasma virus level. Because Th17 cells play a central role in innate and adaptive immune response to extracellular bacteria, our finding may explain the chronic enteropathy in human immunodeficiency virus (HIV) infection. Thus, therapeutic approaches that reconstitute an adequate balance between Th1 and Th17 may be beneficial in the treatment of HIV infection.

PMID: 19079189 [PubMed - indexed for MEDLINE]

J Infect Dis. 2008 Aug 15;198(4):456-64.

Collagen deposition limits immune reconstitution in the gut.

Estes J, Baker JV, Brenchley JM, Khoruts A, Barthold JL, Bantle A, Reilly CS, Beilman GJ, George ME, Douek DC, Haase AT, Schacker TW.

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Comment in:

- J Infect Dis. 2008 Aug 15;198(4):453-5.

Despite suppression of human immunodeficiency virus (HIV) replication by antiretroviral therapy, reconstitution of CD4+ cells is variable and incomplete, particularly in gut-associated lymphatic tissues (GALT). We have previously shown that immune activation and inflammation in HIV-infected and simian immunodeficiency virus-infected lymph nodes results in collagen deposition and disruption of the lymphatic tissue architecture, and this damage contributes to CD4+ cell depletion before treatment and affects the extent of immune reconstitution after treatment. In the present study, we compared collagen deposition and the extent of depletion and reconstitution of total CD4+ cells and subsets in peripheral blood, lymph nodes, and inductive and effector sites in GALT. We show that CD4+ cell depletion in GALT correlates with the rapidity and greater magnitude of collagen deposition in this compartment, compared with that in peripheral lymph nodes, and that although treatment does not restore CD4+ cells to effector sites, treatment in the early stages of infection can increase CD4+ central memory cells in Peyer patches.

PLoS Pathog. 2009 Feb;5(2):e1000295. Epub 2009 Feb 13.

Critical loss of the balance between Th17 and T regulatory cell populations in pathogenic SIV infection.

Favre D, Lederer S, Kanwar B, Ma ZM, Proll S, Kasakow Z, Mold J, Swainson L, Barbour JD, Baskin CR, Palermo R, Pandrea I, Miller CJ, Katze MG, McCune JM.

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Abstract

Chronic immune activation and progression to AIDS are observed after SIV infection in macaques but not in natural host primate species. To better understand this dichotomy, we compared acute pathogenic SIV infection in pigtailed macaques (PTs) to non-pathogenic infection in African green monkeys (AGMs). SIVagm-infected PTs, but not SIVagm-infected AGMs, rapidly developed systemic immune activation, marked and selective depletion of IL-17-secreting (Th17) cells, and loss of the balance between Th17 and T regulatory (Treg) cells in blood, lymphoid organs, and mucosal tissue. The loss of Th17 cells was found to be predictive of systemic and sustained T cell activation. Collectively, these data indicate that loss of the Th17 to Treg balance is related to SIV disease progression.

PMID: 19214220 [PubMed - indexed for MEDLINE]PMCID: PMC2635016Free PMC Article

Supplemental Content

Semin Immunopathol. 2009 Jul;31(2):257-66. Epub 2009 May 30.

Disturbance of the gut-associated lymphoid tissue is associated with disease progression in chronic HIV infection.

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Abstract

Why and how HIV makes people sick is highly debated. Recent evidence implicates heightened immune activation due to breakdown of the gastrointestinal barrier as a determining factor of lentiviral pathogenesis. HIV-mediated loss of Th17 cells from the gut-associated lymphoid tissue (GALT) impairs mucosal integrity and innate defense mechanisms against gut microbes. Translocation of microbial products from the gut, in turn, correlates with increased immune activation in chronic HIV infection and may further damage the immune system by increasing viral and activation-induced T cell death, by reducing T cell reconstitution due to tissue scarring, and by impairing the function of other cell types, such as gammadelta T cells and epithelial cells. Maintaining a healthy GALT may be the key to reducing the pathogenic potential of HIV.

PMID: 19484240 [PubMed - indexed for MEDLINE]

Supplemental Content

Blood. 2008 Oct 1;112(7):2826-35. Epub 2008 Jul 29.

Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections.

Brenchley JM, Paiardini M, Knox KS, Asher AI, Cervasi B, Asher TE, Scheinberg P, Price DA, Hage CA, Kholi LM, Khoruts A, Frank I, Else J, Schacker T, Silvestri G, Douek DC.

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Acute HIV infection is characterized by massive loss of CD4 T cells from the gastrointestinal (GI) tract. Th17 cells are critical in the defense against microbes, particularly at mucosal surfaces. Here we analyzed Th17 cells in the blood, GI tract, and broncheoalveolar lavage of HIV-infected and uninfected humans, and SIV-infected and uninfected sooty mangabeys. We found that (1) human Th17 cells are specific for extracellular bacterial and fungal antigens, but not common viral antigens; (2) Th17 cells are infected by HIV in vivo, but not preferentially so; (3) CD4 T cells in blood of HIV-infected patients are skewed away from a Th17 phenotype toward a Th1 phenotype with cellular maturation; (4) there is significant loss of Th17 cells in the GI tract of HIV-infected patients; (5) Th17 cells are not preferentially lost from the broncheoalveolar lavage of HIV-infected patients; and (6) SIV-infected sooty mangabeys maintain healthy frequencies of Th17 cells in the blood and GI tract. These observations further elucidate the immunodeficiency of HIV disease and may provide a mechanistic basis for the mucosal barrier breakdown that characterizes HIV infection. Finally, these data may help account for the nonprogressive nature of nonpathogenic SIV infection in sooty mangabeys.

Supplemental Content

J Infect Dis. 2009 Apr 15;199(8):1177-85.

Plasma levels of bacterial DNA correlate with immune activation and the magnitude of immune restoration in persons with antiretroviral-treated HIV infection.

Jiang W, Lederman MM, Hunt P, Sieg SF, Haley K, Rodriguez B, Landay A, Martin J, Sinclair E, Asher AI, Deeks SG, Douek DC, Brenchley JM.

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Erratum in:

- J Infect Dis. 2009 Jul 1;200(1):160.

The significance of elevated plasma levels of bacterial lipopolysaccharide (LPS) in persons with chronic HIV infection remains undefined. We measured LPS levels by use of limulus lysate assay, and DNA sequences encoding bacterial ribosomal 16S RNA (16S rDNA) were assessed by quantitative polymerase chain reactions in plasma samples obtained from 242 donors. Plasma levels of 16S rDNA were significantly higher in human immunodeficiency virus (HIV)-infected subjects than in uninfected subjects, and they correlated with LPS levels. Higher levels of 16S rDNA were associated with higher levels of T cell activation and with lower levels of CD4 T cell restoration during antiretroviral therapy. Antiretroviral therapy

reduces but does not fully normalize plasma levels of bacterial 16S rDNA, an index of microbial translocation from the gastrointestinal tract. High levels of 16S rDNA during therapy are strongly associated with reduced increases in the CD4(+) T lymphocyte count, irrespective of plasma HIV RNA levels. These findings are consistent with the importance of microbial translocation in immunodeficiency and T cell homeostasis in chronic HIV infection.

PMID: 19265479 [PubMed - indexed for MEDLINE]

Supplemental Content

PLoS Pathog. 2009 Apr;5(4):e1000372. Epub 2009 Apr 10.

Association of progressive CD4(+) T cell decline in SIV infection with the induction of autoreactive antibodies.

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The progressive decline of CD4(+) T cells is a hallmark of disease progression in human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) infection. Whereas the acute phase of the infection is dominated by virus-mediated depletion of memory CD4(+) T cells, chronic infection is often associated with a progressive decline of total CD4(+) T cells, including the naïve subset. The mechanism of this second phase of CD4(+) T cell loss is unclear and may include immune activation-induced cell death, immune-mediated destruction, and regenerative or homeostatic failure. We studied patterns of CD4(+) T cell subset depletion in blood and tissues in a group of 20 rhesus macaques inoculated with derivatives of the pathogenic SIVsmE543-3 or SIVmac239. Phenotypic analysis of CD4(+) T cells demonstrated two patterns of CD4(+) T cell depletion, primarily affecting either naïve or memory CD4(+) T cells. Progressive decline of total CD4(+) T cells was observed only in macaques with naïve CD4(+) T cell depletion (ND), though the depletion of memory CD4(+) T cells was profound in macaques with memory CD4(+) T cell depletion (MD). ND macaques exhibited lower viral load and higher SIV-specific antibody responses and greater B cell activation than MD macaques. Depletion of naïve CD4(+) T cells was associated with plasma antibodies autoreactive with CD4(+) T cells, increasing numbers of IgG-coated CD4(+) T cells, and increased incidence of autoreactive antibodies to platelets (GPIIIa), dsDNA, and phospholipid (aPL). Consistent with a biological role of these antibodies, these latter antibodies were accompanied by clinical features associated with autoimmune disorders, thrombocytopenia, and catastrophic thrombotic events. More importantly for AIDS pathogenesis, the level of autoreactive antibodies significantly correlated with the extent of

naïve CD4(+) T cell depletion. These results suggest an important role of autoreactive antibodies in the CD4(+) T cell decline observed during progression to AIDS.

Supplemental Content

Curr Opin HIV AIDS. 2008 May;3(3):356-61.

The mucosal barrier and immune activation in HIV pathogenesis.

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PURPOSE OF REVIEW: Significant gastrointestinal pathology occurs in progressive HIV and simian immunodeficiency virus (SIV) infections. This review will examine the relationship between the detrimental events to the gastrointestinal tract during the acute phase of infection and disease progression through the chronic phase and, ultimately, AIDS. RECENT FINDINGS: Gastrointestinal tract CD4 T cells are dramatically depleted in acutely HIV-infected humans and SIV-infected rhesus macaques, sooty mangabeys, and African green monkeys. In addition HIV infection of humans and SIV-infection of rhesus macaques are characterized by enteropathy and increased intestinal permeability. While SIV-infected rhesus macaques and HIV-infected humans manifest chronic and systemic immune activation and microbial translocation, and progress to chronic infection and AIDS, however, SIV-infected sooty mangabeys and African green monkeys do not. SUMMARY: Recent studies have increased our understanding of the mechanisms relating structural and immunological damage to the gastrointestinal tract during the acute phase of HIV/SIV infection to immune activation and disease progression in the chronic phase.

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PMCID: PMC2789390

Supplemental Content

J Immunol. 2008 Nov 15;181(10):6687-91.

Cutting edge: Experimentally induced immune activation in natural hosts of

simian immunodeficiency virus induces significant increases in viral replication and CD4+ T cell depletion.

Pandrea I, Gaufin T, Brenchley JM, Gautam R, Monjure C, Gautam A, Coleman C, Lackner AA, Ribeiro RM, Douek DC, Apetrei C.

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Chronically SIVagm-infected African green monkeys (AGMs) have a remarkably stable nonpathogenic disease course, with levels of immune activation in chronic SIVagm infection similar to those observed in uninfected monkeys and with stable viral loads for long periods of time. In vivo administration of LPS or an IL-2/diphtheria toxin fusion protein (Ontak) to chronically SIVagm-infected AGMs triggered increases in immune activation and subsequently of viral replication and depletion of intestinal CD4(+) T cells. Our study indicates that circulating microbial products can increase viral replication by inducing immune activation and increasing the number of viral target cells, thus demonstrating that immune activation and T cell proliferation are key factors in AIDS pathogenesis.

PMID: 18981083 [PubMed - indexed for MEDLINE]

Supplemental Content

Nat Med. 2006 Dec;12(12):1365-71. Epub 2006 Nov 19.

Microbial translocation is a cause of systemic immune activation in chronic HIV infection.

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.

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Comment in:

- Nat Med. 2006 Dec;12(12):1351-2.

Chronic activation of the immune system is a hallmark of progressive HIV infection and better predicts disease outcome than plasma viral load, yet its etiology remains obscure. Here we show that circulating microbial products, probably derived from the gastrointestinal tract, are a cause of HIV-related systemic immune activation. Circulating lipopolysaccharide, which we used as an indicator of microbial translocation, was significantly increased in chronically HIV-infected individuals and in simian immunodeficiency virus (SIV)-infected rhesus macaques (P <or= 0.002). We show that increased lipopolysaccharide is bioactive in vivo and correlates with measures of innate and adaptive immune activation. Effective antiretroviral therapy seemed to reduce microbial translocation partially. Furthermore, in nonpathogenic SIV infection of sooty mangabeys, microbial translocation did not seem to occur. These data establish a mechanism for chronic immune activation in the context of a compromised gastrointestinal mucosal surface and provide new directions for therapeutic interventions that modify the consequences of acute HIV infection.

PMID: 17115046 [PubMed - indexed for MEDLINE]

Supplemental Content