HIV Pathogenesis: The Host

A.A. Lackner¹, Michael M. Lederman², and Benigno Rodriguez²

¹Tulane National Primate Research Center, Tulane University Health Science Center, Covington, Louisiana 70443

²Department of Molecular Biology and Microbiology, Case Western Reserve University, Cleveland, Ohio 44106

Correspondence: alackner@tulane.edu

Human immunodeficiency virus (HIV) pathogenesis has proven to be quite complex and dynamic with most of the critical events (e.g., transmission, CD4⁺ T-cell destruction) occurring in mucosal tissues. In addition, although the resulting disease can progress over years, it is clear that many critical events happen within the first few weeks of infection when most patients are unaware that they are infected. These events occur predominantly in tissues other than the peripheral blood, particularly the gastrointestinal tract, where massive depletion of CD4⁺ T cells occurs long before adverse consequences of HIV infection are otherwise apparent. Profound insights into these early events have been gained through the use of nonhuman primate models, which offer the opportunity to examine the early stages of infection with the simian immunodeficiency virus (SIV), a close relative of HIV that induces an indistinguishable clinical picture from AIDS in Asian primate species, but importantly, fails to cause disease in its natural African hosts, such as sooty mangabeys and African green monkeys. This article draws from data derived from both human and nonhuman primate studies.

Untreated, about half of HIV-infected persons will develop major opportunistic complications reflective of profound immune deficiency within 10 years of acquiring infection; some succumb within months, yet others remain well as long as 20 years or more after acquiring infection. Occasional variability in disease course may be owing to variations in HIV itself; rare deletions in the *nef* gene have been associated with a slower disease course (Deacon et al. 1995; Kirchhoff et al. 1995) and even less frequently, mutations in the *vpr* gene have been found in some slow progressors (Lum et al. 2003).

Host defenses undoubtedly play an important role in the course of HIV disease. The importance of diversity of T-cell recognition in disease control was suggested by the observation that homozygosity for class I human leukocyte antigen (HLA) molecules is associated with an accelerated disease course (Carrington et al. 1999; Tang et al. 1999). More specifically, certain class I HLA types (Goulder et al. 1996; Kaslow et al. 1996) are associated with a more benign disease course, whereas others (Kaslow et al. 1990) are associated with a more aggressive disease course. Genetic analyses also have implicated natural killer cells and their ligands as

Editors: Frederic D. Bushman, Gary J. Nabel, and Ronald Swanstrom
Additional Perspectives on HIV available at www.perspectivesinmedicine.org

Copyright © 2012 Cold Spring Harbor Laboratory Press; all rights reserved; doi: 10.1101/cshperspect.a007005
Cite this article as *Cold Spring Harb Perspect Med* 2012;2:a007005

A.A. Lackner et al.

important genetic determinants of disease outcome (Martin et al. 2002). Other host elements appear to be important in determining the course of disease. Although persons who are homozygous for a 32-base-pair deletion in CCR5 are nearly completely protected from acquiring HIV infection (Dean et al. 1996; Liu et al. 1996; Samson et al. 1996), heterozygous individuals are infectible, yet their course tends to be less aggressive (Ioannidis et al. 2001).

A very small proportion of infected persons manage to control HIV replication in the absence of antiretroviral therapy. Although rare persons with relatively slowly progressive disease have been infected with defective viruses as indicated above, these “elite controllers” appear to be infected with viruses that are fully replication competent and lacking unique signatures (Blankson et al. 2007; Miura et al. 2008). Humoral defenses mediated by neutralizing antibodies do not appear to mediate control of viral replication (Bailey et al. 2006), but evidence to date implicates T-cell-mediated responses to HIV as important determinants of elite control. Approximately half of these elite controllers express HLA-B*57, HLA-B*5801, or HLA-B*27 (Emu et al. 2008), implicating HLA-class I–restricted recognition of HIV peptides as important in control of HIV replication. The quality of these T-cell responses also may be important as elite controllers tend to have CD8⁺ T cells that are polyfunctional in terms of their ability to express cytokines and degranulate after HIV peptide stimulation (Migueles et al. 2002, 2008; Betts et al. 2006; Emu et al. 2008; Owen et al. 2010).

Our understanding of the pathogenesis of AIDS has evolved dramatically since its initial discovery. Although originally thought to involve a period of viral latency, it is now clear that HIV replication occurs at a high level throughout infection and that there is a highly dynamic interplay between the host immune response, attempts by the host to replenish cells that are destroyed, as well as virus and viral evolution that appear to differ among various tissue compartments (Horton et al. 2002; Paranjpe et al. 2002; Ryzhova et al. 2002; Gonzalez-Scarano and Martin-Garcia 2005). Progress in defining

both molecular and cellular viral targets of HIV infection has also led to important discoveries that allow us to better understand the various stages of infection as well as the events leading to immunodeficiency. The cellular receptors for HIV and SIV are the CD4 molecule on T cells and monocyte/macrophage lineage cells along with a chemokine receptor; most commonly CCR5 and CXCR4 (Alkhatib et al. 1996; Moore et al. 2004). In humans, infection is typically established by virus that uses CCR5 for cellular entry, but with time, viruses often emerge that are capable of using another receptor, CXCR4, for infection of target cells (Koot et al. 1999). These viruses become more prevalent with advanced disease and although it is likely that advancing immune deficiency predisposes to the emergence of these variants, CXCR4 is more broadly expressed by human CD4 T cells than is CCR5, and the emergence of CXCR4 using viruses in untreated infection is often associated with an accelerated disease course. Infection of CD4⁺ T cells may lead to their destruction (even without productive infection for CXCR4 using viruses [Doitsh et al. 2010]). Infection of monocyte/macrophage lineage cells is also important, as these are likely major reservoirs for viral replication and persistence, and may also contribute to disease progression, immune deficiency, and AIDS-associated syndromes in nonlymphoid organs such as the brain, heart, and kidney (Shannon 2001; Ross and Klotman 2004; Hasegawa et al. 2009).

HISTORY

Clinical Manifestations of HIV Infection

Most persons who become HIV infected experience an illness characterized often by fever, sore throat, lymphadenopathy, and rash (Schacker et al. 1996). These symptoms are often severe enough that persons will seek medical attention, but as they are nonspecific and self-limited, they are often attributed to nonspecific viral infections, and testing for HIV is often not performed. In the first few weeks of infection, levels of serum antibodies to HIV proteins are typically not sufficiently elevated to permit

diagnosis of infection by enzyme-linked immunosorbent assay (ELISA) and immunoblot, but high levels of HIV RNA are readily detectable in plasma. During these first few weeks of infection, there is profound destruction of CCR5⁺ CD4⁺ memory cells in gut tissue in both SIV and HIV infection (Veazey et al. 1998; Brenchley et al. 2004b), but interestingly, gastrointestinal symptoms are not common during this period in HIV infection (Schacker et al. 1996). High-level viremia typically diminishes as acute infection symptoms resolve and a “set point” of viremia is established that varies from rare elite controllers in whom virus levels in plasma are typically below levels of detection by commercial assays (<40 copies/mL) to levels in excess of 100,000 copies per mL. With resolution of symptoms, the HIV-infected person may be completely without signs or symptoms of disease, yet most will experience progressive depletion of CD4⁺ T cells from circulation and from lymph nodes. Most persons will remain free of AIDS-defining illness until the circulating CD4 T-cell count falls to levels of 200 cells/ μ L or lower. Although persons with higher levels of virus in plasma tend to progress to the immune deficiency of AIDS more rapidly (Mellors et al. 1996, 1997), the magnitude of viremia is an incomplete predictor of the pace of disease progression (Rodriguez et al. 2006) and it appears that markers of systemic immune activation are useful predictors of disease progression risk (Giorgi et al. 1993; Liu et al. 1996; Deeks et al. 2004).

The clinical complications of advanced untreated HIV infection typically comprise infectious or malignant complications reflective of the profound impairments in T-cell-mediated immunity. Thus infections attributable to organisms such as *Pneumocystis jirovecii*, mycobacteria, cytomegalovirus, *Toxoplasma gondii*, and Cryptococcus as well as the occurrence of malignancies related to viral pathogens such as non-Hodgkins lymphoma and Kaposi's sarcoma are common. Nonetheless, the profound immune deficiency also affects humoral defenses, placing infected persons at increased risk for infection with pathogens like *Streptococcus pneumoniae* (Janoff et al. 1992; Hirschtick et al. 1995). With effective suppression of HIV

replication after administration of antiretroviral therapies, immune function typically improves and risks for these life-threatening complications diminish. In the current era and where there is broad access to effective combination antiretroviral therapies, the predicted survival of the HIV-infected patient can approach that of the general population if treatment is initiated early in the course of infection (Antiretroviral Therapy Cohort Collaboration 2008; van Sighem et al. 2010). In the current era, cardiovascular disease, serious liver disease related to coinfection with hepatitis viruses, renal insufficiency, and a changing spectrum of malignant disorders are major causes of morbidity and mortality in HIV infection (Palella et al. 2006; Marin et al. 2009; Hasse et al. 2011).

Early Recognition of Key Aspects of Pathogenesis in Humans

With the first reports of AIDS, astute clinicians recognized that impairments in host defenses must underlie the opportunistic infections they were seeing (Gottlieb et al. 1981; Masur et al. 1981; Siegal et al. 1981). Thus, profound depletion of CD4 T cells was recognized immediately (Gottlieb et al. 1981; Masur et al. 1981; Siegal et al. 1981) as was dysregulation of B-cell function (Lane et al. 1983). Interestingly, early investigators also recognized that despite profound immune deficiency, immune cells also showed evidence of immune activation (Gottlieb et al. 1981; Lane et al. 1983). With the identification of HIV (Barre-Sinoussi et al. 1983; Gallo et al. 1984; Levy et al. 1984) and the recognition that infection of CD4 T cells was cytopathic (Zagury et al. 1986), a key mechanism for circulating CD4⁺ T-cell losses was reasonably imputed. The central role of viral replication in CD4 T-cell losses and immune deficiency was further confirmed by the reliable increases in CD4 T-cell numbers and enhancement of immune function with administration of suppressive antiretroviral therapies (Autran et al. 1997; Lederman et al. 1998). Nonetheless, the precise mechanisms whereby infection with HIV resulted in progressive immune deficiency remained ill defined. Indirect mechanisms for

A.A. Lackner et al.

cell loss were suggested by the relative infrequency with which circulating blood and lymph node cells could be shown to be HIV infected (Douek et al. 2002). The role and potential importance of immune activation in disease pathogenesis was suggested by epidemiologic studies in which markers of immune activation proved powerful predictors of the risk of disease progression (Giorgi et al. 1993, 1999; Liu et al. 1997, 1998; Hazenberg et al. 2003; Deeks et al. 2004; Wilson et al. 2004).

Cellular Targets for SIV/HIV

HIV and SIV use a two-receptor model for infection that requires both CD4 and a chemokine receptor that results in CD4⁺ T cells and monocyte/macrophage lineage cells being the primary targets for infection. In addition, the activation state of CD4⁺ T lymphocytes has a significant impact on the ability of the virus to replicate successfully. As newly produced lymphocytes emerge from the thymus, they are generally considered “naïve” in that they have never encountered their cognate antigen and are thus in a “resting” state. Naïve, resting cells are abundant in the blood and in organized lymphoid tissues (lymph nodes, intestinal Peyer’s patches, etc.). Cells that have previously encountered their antigen are considered memory cells, which can be distinguished by expression of specific cell-surface antigens. In addition, memory cells can also be subdivided into short-lived, “effector memory” cells, which are actively secreting cytokines, and/or long-lived “central” memory cells, which may be “resting” or rapidly activated to mount immune responses on further exposure to the antigen. Activated CD4⁺ T cells, identified in part by expression of CD25, CD69, HLA-DR, etc., are able to support HIV and SIV infection quite well, whereas resting CD4⁺ T cells, and especially naïve CD4 T cells, do not (Stevenson et al. 1990; Zack et al. 1990; Chou et al. 1997). In part this may be because resting naïve CD4⁺ T cells generally do not express CCR5 and thus are resistant to SIV and to HIV, viruses that typically use CCR5 for cellular entry. However, resting central memory cells, which express low levels of CCR5, have been shown

to be significant targets for SIV in vivo (Li et al. 2005). In addition, activated cells are generally transcribing DNA, which logically would promote more viral replication.

KEY ADVANCES

Mucosal Tissues and HIV Infection

It is now evident in SIV-infected macaques and HIV-infected humans that mucosal tissues are not only primary sites of viral transmission but also the major sites for viral replication and CD4⁺ T-cell destruction, regardless of route of transmission. Furthermore, intestinal mucosal tissues appear to be major sites of HIV/SIV persistence even after administration of suppressive antiretroviral therapies (Chun et al. 2008). Understanding the basis of this central role of mucosal tissues in the pathogenesis of AIDS is critical for efforts to develop strategies to prevent or treat AIDS.

General features of mucosal immune system. The intestinal immune system is considered the largest single immunologic organ in the body containing upwards of 40% of all lymphocytes (Schieferdecker et al. 1992; MacDonald and Spencer 1994). Thus, when considering the rest of the mucosal immune system, including the lungs, reproductive tract, urinary tract, mammary glands, etc., it is clear that the mucosal immune system dwarfs the systemic immune system. Furthermore, in contrast to the systemic immune system, most of the CD4⁺ T cells in the mucosal immune system are CCR5⁺, activated memory CD4⁺ T cells. This is of enormous importance with respect to the pathogenesis of AIDS because these represent the preferred cellular target for HIV/SIV infection (Veazey et al. 2002; Brenchley et al. 2004b; Mehandru et al. 2004). This is also reflected in the fact that productive infection of peripheral CD4⁺ T cells is rare (0.01%–1%) (Brenchley et al. 2004a), whereas infection of mucosal CD4 cells is quite common with estimates of 60% of mucosal memory CD4⁺ cells infected within days of infection (Mattapallil et al. 2005).

The unique challenges faced by the mucosal tissues and the immune system have resulted in

a structurally and functionally distinct mucosal immune system. In the case of the intestine, this includes both inductive, organized lymphoid tissues and diffuse effector lymphoid tissues. The inductive sites in the intestine and most other mucosal sites include widely scattered but well-organized lymphoid follicles best exemplified by solitary and aggregated (Peyer's patches) lymphoid follicles. In general, these are found in the tonsils, the terminal portion of the small intestine (particularly the ileum), as well as the terminal portion of the large intestine (rectum), cecum, and appendix.

In addition to the organized lymphoid tissues of the inductive arm of the mucosal immune system, there is an even larger pool of immune cells diffusely scattered throughout mucosal tissues that serves as the "effector" arm of the mucosal immune system (Mowat and Viney 1997). The effector arm consists of large numbers of various subsets of lymphocytes, macrophages, dendritic cells, and other immune cells that are scattered diffusely throughout the lamina propria and epithelium of mucosal tissues (Mowat and Viney 1997). These cells are responsible for carrying out the major effector functions of the intestinal immune response that are "initiated" in inductive sites.

Immunophenotypic composition of the mucosal immune system. As mentioned above, mucosal tissues contain the majority of all the lymphocytes and macrophages in the body. From an anatomic perspective, the lymphocyte populations can be divided into those present in epithelium (intraepithelial lymphocytes [IEL]) and those in the underlying lamina propria (lamina propria lymphocytes [LPL]). The LPL can be further subdivided into those from inductive sites (organized lymphoid nodules) and effector sites (diffuse lamina propria). More than 90% of the IEL are CD3⁺ T cells, ~80% of which express CD8 (Mowat and Viney 1997; Veazey et al. 1997). In addition, ~10% of IEL express the $\gamma\delta$ T-cell receptor (TCR) (Viney et al. 1990). In contrast, the phenotype of lymphocytes in the lamina propria is remarkably different, with most lymphoid phenotypes being represented (Mowat and Viney 1997). Most importantly, the lamina propria of mucosal tissues

contains a vast reservoir of CD4⁺ T cells. In normal humans and nonhuman primates, the ratio of CD4⁺ to CD8⁺ T cells in the lamina propria is similar to that in peripheral blood and lymph nodes (Mowat and Viney 1997; Veazey et al. 1997; Veazey 2003). However, in contrast to peripheral lymphoid tissues, a much larger percentage of mucosal CD4⁺ T cells express CCR5, have a memory phenotype, and express markers of activation particularly when examining LPL from the diffuse lamina propria separately from organized lymphoid nodules (James et al. 1987; Zeitz et al. 1988; Schieferdecker et al. 1992; Mowat and Viney 1997; Veazey et al. 1997, 1998). Furthermore, a large percentage of CD4⁺ T cells also produce cytokines in situ, indicating that they are activated, terminally differentiated effector cells (Mowat and Viney 1997).

Combined, these data indicate that the largest pool of activated, terminally differentiated, memory CCR5⁺CD4⁺ T cells resides in mucosal tissues (particularly the diffuse lamina propria) and not in peripheral blood or lymph nodes. HIV and SIV preferentially infect these memory CCR5⁺CD4⁺ T cells in immune effector sites (diffuse lamina propria), causing rapid depletion of these cells by 21 d after infection. Subsequently, most infected cells in the intestine are present in immune inductive sites represented by organized lymphoid nodules in the lamina propria (Veazey et al. 1998, 2000b, 2001b). This dramatic and rapid loss of CD4⁺ T cells in mucosal effector sites in SIV-infected macaques is associated with subclinical opportunistic infections as well as significant alterations in intestinal structure and function (Heise et al. 1994; Stone et al. 1994). In humans, symptomatic disease of the intestine is rare in early HIV infection, yet the early damage to this important defense system may play a key role in both progressive immune deficiency and immune dysregulation.

Of additional importance is a subset of CD4⁺ T cells known as Th17 cells because they produce IL-17 and IL-22 but not interferon γ or IL-4 (Steinman 2007). Of particular relevance for this discussion is the role these cells likely play in enterocyte homeostasis and production of antimicrobial defensins, both of

A.A. Lackner et al.

which are critical for maintenance of the mucosal barrier (Kolls and Linden 2004; Liang et al. 2006). Recent evidence indicates that Th17 cells are even more profoundly depleted in the intestinal mucosa of HIV- and SIV-infected individuals than the general CD4⁺ CCR5⁺ T-cell population (Brenchley et al. 2008; Favre et al. 2009). Thus, the loss of these Th17 cells provides a possible direct link between CD4⁺ T-cell destruction and dysfunction of the intestinal mucosa.

Interactions between the mucosal immune system and intestinal structure and function. Alterations in intestinal structure and function associated with HIV/SIV infection has long been recognized (Batman et al. 1989; Ullrich et al. 1989; Cummins et al. 1990; Heise et al. 1993, 1994). Histologically, villus atrophy and increased epithelial apoptosis in the villus tips was often linked to increased proliferation of crypt cells leading to crypt hyperplasia. This lesion of “crypt hyperplastic villous atrophy” had been associated with mucosal T-cell activation in vitro (MacDonald and Spencer 1988; Ferreira et al. 1990; Field 2006; Turner 2009). However, in the case of AIDS, the dominant recognized feature was one of immune suppression rather than activation, although even the earliest reports of AIDS in humans provide evidence of immune activation (Gottlieb et al. 1981; Masur et al. 1981). Over time, however, it was recognized that immune activation is a major feature of SIV and HIV infection and that intestinal immune dysfunction can result in structural changes to the intestinal mucosa and cause breakdown of the intestinal epithelial barrier (MacDonald and Spencer 1992; Clayburgh et al. 2004; Kolls and Linden 2004; Liang et al. 2006; Weber and Turner 2007; Estes et al. 2010). The molecular basis for damage to the intestinal epithelial barrier is now beginning to come into focus aided by functional genomics approaches and their frequent application to studies of AIDS pathogenesis.

Normal function of the mucosal barrier requires not only an intact epithelium joined by tight junctions, but also coordinated function of multiple cell types that occupy distinct anatomical positions and maintain reciprocal

interrelationships (Traber 1997; Turner 2009). The sudden and massive destruction of activated effector memory CD4⁺, CCR5⁺ cells, and Th17 cells would be expected to disrupt this communication network linking epithelial cells and the intestinal immune system (Shanahan 1999). A consequence of this disruption is likely deprivation of epitheliotropic factors required for epithelial cell growth, maintenance, and renewal leading to increased epithelial cell apoptosis and death. In support of this concept, significant down-modulation of genes regulating intestinal epithelial cell growth and renewal along with increased expression of inflammation and immune activation genes, and activated caspase 3 protein expression in epithelial cells has been observed in primary HIV infection (Sankaran et al. 2005, 2008; George et al. 2008). Additionally, increases in proinflammatory cytokine production in the colon as early as 6–10 d post-SIV infection (Abel et al. 2005) and in the intestine of HIV-infected patients (Reka et al. 1994; Olsson et al. 2000; McGowan et al. 2004) may further facilitate mucosal damage by activating myosin light chain kinase (MLCK), which has been implicated as a major player in initiating damage to the intestinal epithelial barrier (Turner 2006, 2009).

Early Targets of Infection, Amplification, and Viral Dissemination

Although HIV/SIV may undergo limited replication within dendritic cells in mucosal surfaces that contain them (vagina, anus, tonsil—all lined by stratified squamous epithelium) (Spira et al. 1996; Hu et al. 2000), the primary substrate for HIV/SIV replication is memory CD4⁺ T cells expressing CCR5 (hereafter referred to as “primary target cells”). How the virus reaches these cells, which are abundant in the lamina propria of all mucosal tissues, varies depending on the route and site of transmission.

In the case of the rectal mucosa, once the virus crosses the epithelium, either via small mucosal breaks or via M cells, the virus will encounter a high density of primary target cells to support significant levels of viral replication (amplification). It is particularly worth noting

that M cells form an intraepithelial pocket containing CD4⁺ memory cells and dendritic cells, which would greatly facilitate HIV/SIV replication (Pope et al. 1994; Neutra et al. 1996). After local replication and amplification, it is likely that virus and viral-infected cells will migrate to draining lymph nodes and from there to the rest of the body.

For transmission via the vagina (and presumably the anus), intraepithelial dendritic cells appear to play a major role. Although there are significant numbers of primary target cells in the vaginal lamina propria (Veazey et al. 2003), there are also data that indicates that dendritic cells can rapidly carry virus to regional lymph nodes (Hu et al. 2000). In this case, it appears that spread to regional lymph nodes occurs before there is significant local replication of virus in the vaginal lamina propria. This is likely because the virus is subverting normal trafficking patterns of intraepithelial dendritic cells that bring antigen to immune inductive sites (regional lymph nodes), which are lacking in the vaginal mucosa as compared with intestinal mucosa.

Although SIV can be found in draining lymph nodes within 18 h of vaginal inoculation, it is interesting to note that a delay in viremia often occurs with mucosal inoculation compared with intravenous inoculations of macaques (Ma et al. 2004; Miller et al. 2005). This likely occurs because the virus has to replicate locally for a period of time to generate sufficient progeny to cause a spreading infection or, in the case of the vagina, because of the low density of primary target cells that would be found in a regional lymph node. Although lymph nodes contain a high density of lymphocytes, unless that node is draining a site of inflammation, the vast majority of the T cells will be CCR5⁻, resting, and naïve, and thus relatively resistant to infection. In support of this, Miller et al. (2005) have shown focal viral replication occurring in the lamina propria of cervicovaginal tissues before productive systemic infection, suggesting that local viral replication at the site of exposure was necessary to amplify virus before systemic infections could proceed.

In contrast to mucosal transmission, which provides a selective barrier based on the ability

of the virus to contact target cells either directly or by using existing biological processes, intravenous transmission poses no such barrier. Thus, the virus quickly disseminates to all tissues, including those that support high levels of viral replication (mucosal tissues). Viremia can be detected as early as 2–3 d after intravenous infection in macaques, with peak viremia occurring 10–14 d after intravenous infection. At the time of peak viremia, virus can be found in lymphoid tissues throughout the body including thymus, spleen, peripheral lymphoid organs, and mucosal lymphoid tissues. In addition, virus is readily found in the central nervous system by 14 d after infection. Although virus is readily found in tissues by 14 d after infection, it is difficult to find infected cells in tissues by *in situ* hybridization or immunohistochemistry before that time, except in effector sites in mucosal lymphoid tissues such as the lamina propria of the intestinal tract, where significant numbers of productively infected cells have been detected within 3–4 d of intravenous inoculation (Sasseville et al. 1996). Combined, these data suggest that replication in mucosal tissues is not only important for transmission, but also critical for initial viral replication and amplification, regardless of the route of transmission.

Systemic Lymphoid Tissues

By 2 wk after intravenous inoculation of macaques with pathogenic SIV, the virus is widely distributed and easily found in all lymphoid organs. Within these tissues, evidence of productive infection is first seen in individual cells in the paracortex of the lymph nodes, periarteriolar lymphoid sheaths in the spleen (where T cells predominate), and in the thymic medulla, which contains mature lymphocytes as opposed to the thymic cortex. Recent work has shown that within these tissues at these early time points, the primary targets are memory phenotype CCR5⁺ CD4⁺ T cells just as they are in mucosal tissues (Veazey et al. 2000a; Mattapallil et al. 2005). The primary difference is that these cells represent a minority of the cells present in systemic lymphoid tissues.

A.A. Lackner et al.

Between 2 and 3 wk after infection, the picture changes somewhat. Although the majority of infected cells in lymphoid tissues are still CD4⁺ T cells, infection of macrophages becomes readily apparent. This is generally thought to be a result of viral evolution, particularly in the case of cloned viruses such as SIVmac239, which does not readily infect macrophages in vitro.

In addition to infection of macrophages, diffuse labeling for viral RNA and protein over germinal centers in lymphoid organs (referred to as a “follicular” pattern) generally appears in this same time frame. This is largely owing to trapping of antigen/antibody complexes that contain intact virions on follicular dendritic cells. It has been hypothesized that this pool of virions on follicular dendritic cells may represent a major reservoir of infectious HIV-1 (Haase et al. 1996). The appearance of abundant virus on follicular dendritic cells is dependent on the generation of a humoral immune response, which probably occurs more consistently in humans than in macaques where up to 25% or more of the animals mount very poor immune responses and progress to disease quite rapidly (200 d or less) (Westmoreland et al. 1998).

Infection of the thymus is of particular interest because of its role in T-cell renewal. It is well established that dramatic thymic dysinvolution occurs in both HIV-infected humans and SIV-infected macaques. This led to the hypothesis that loss of thymic function was at least partially responsible for the decline in CD4⁺ T cells that accompanies AIDS progression. During the first few weeks of infection, significant changes in cell proliferation, apoptosis, and percentages of T-cell precursors are observed in the thymus coincident with the presence of infected cells and primary viremia (Wykrzykowska et al. 1998). Of particular interest is the marked rebound in T-cell progenitors accompanied by increased levels of cell proliferation in the thymus. This occurred in the face of persistent high-level virus replication and provides strong evidence that the thymus has significant regenerative capacity through at least the first 2 mo of infection. However, by

24 wk of infection, morphologic evidence of severe thymic damage is evident in most SIV-infected animals (but can occur earlier in rapid progressors) (Lackner 1994). The length of this apparent window during which the thymus can regenerate is of importance when considering when to start antiretrovirals and for immune restoration strategies. Data from nonhuman primate studies imply that if combination drug therapy for HIV is not started early enough in infection, limited T-cell regeneration will occur with minimal help from the thymus, mostly as the result of clonal expansion of preexisting cells, resulting in a limited T-cell repertoire. Although much of these data would suggest that the thymus should be important in regeneration, infection studies in thymectomized macaques clearly show that the thymus has little if any role to play in disease progression or the rate of CD4⁺ T-cell depletion in SIV-infected macaques (Arron et al. 2005). In humans with HIV infection, there is ample evidence of thymic dysfunction as characterized by diminished numbers of recent thymic emigrants and circulating naïve T cells (Douek et al. 1998; Dion et al. 2007), and these indices are linked to the outcome of infection both in the absence and presence of antiretroviral therapy (Dion et al. 2007). Yet in small numbers of humans with HIV infection who had had thymectomy, the course of infection did not appear dramatically altered (Haynes et al. 1999).

Early Immune Response

It is now clear that both HIV and SIV selectively infect and destroy memory CD4⁺ T cells (both central and effector cells) resulting in subsequent impairment of immune responses to not only the infecting virus, but to other antigens as well. This tropism for memory CD4⁺ T cells eventually leads to the profound immunodeficiency of AIDS and likely underlies the fact that effective immunity resulting in clearance of the infection has yet to be documented in an HIV-infected patient. This rapid and profound elimination of memory CD4⁺ T cells in infected hosts undoubtedly affects the immune system from the onset, but understanding these

consequences is confounded at least in part by the compartmentalization, dynamics, and resilience of the immune system, especially in mucosal tissues.

Acute SIV infection elicits early and relatively robust immune responses in SIV-infected macaques. Within 1–4 wk of SIV infection, marked increases in CD8⁺ (fivefold to 10-fold) and natural killer (NK) cell (two- to threefold) proliferation are observed in the blood (Kaur et al. 2000). Interestingly, most of this proliferation appears to be nonspecific as few of the responding CD8⁺ T cells can be shown to be specific for SIV antigens during peak viremia (Veazey et al. 2003a). Similarly, few of the CD8⁺ T cells and even fewer CD4⁺ T cells are demonstrably virus specific in HIV-infected patients (Betts et al. 2001). This discrepancy may be in part owing to the specificity of current assays, but is more likely a result of immune activation mediated through the destruction of infected cells or through cytokines/chemokines produced by cells directly responding to antigens or viral gene products (Grossman et al. 2006).

Mucosal tissues are also a major site for generation of virus-specific immune responses. Using tetramer technology in genetically defined macaques, strong virus-specific cytotoxic T-lymphocyte (CTL) responses are detected in mucosal sites within 14–21 d of infection (Veazey et al. 2003a; Reynolds et al. 2005). In both intravenously and rectally inoculated macaques, virus-specific CTLs appear to emerge simultaneously in blood and intestines, although the percentages of mucosal CTLs often exceed those in the blood in both early and chronic infection (Veazey et al. 2001a, 2003a; Stevceva et al. 2002). Interestingly, few virus-specific CTLs were detected in the gut of vaginally inoculated animals using similar (tetramer) techniques (Reynolds et al. 2005), which could reflect differences in CTL development or homing depending on the route of transmission, but this remains to be fully explored. In addition to cell-mediated immune responses, infection with SIV or HIV also results in generation of diverse antibody responses, although some strains of SIV are quite poor at eliciting neutralizing antibodies.

Regardless, neither robust cellular nor humoral immune responses are sufficient to clear the infection, and correlates of effective immunity to SIV and HIV remain to be determined.

Although there is consensus that early infection with SIV and HIV results in robust early immune responses, it is also apparent that the magnitude as well as quality of the immune response diminishes with time. In humans, CTL-mediated killing is more rapid in early versus chronic HIV infection (Asquith et al. 2006). Moreover, CD4⁺ immune responses to tetanus toxoid and hepatitis C virus (in coinfecting patients) also decline as the disease progresses (Harcourt et al. 2006). In the animal model of pathogenic HIV infection, studies using tetramer technology have shown that the levels of SIV-specific CTL diminish with time (Veazey et al. 2003a). Thus, both human and animal data suggest that the development of AIDS occurs gradually despite the fact that most of the memory CD4⁺ T cells are eliminated within days of infection and never fully restored, at least in animals that progress to AIDS. This may be partly explained by the fact that, in the majority of animals, sustained increases in CD4⁺ T-cell turnover throughout SIV infection usually result in maintenance of “threshold levels” of mucosal CD4⁺ T cells (5%–10% of normal values), which seems sufficient to maintain immune function, although subclinical opportunistic infections are frequently found in macaques within weeks of infection (Lackner et al. 1994). Therefore, the ongoing destruction of memory CD4⁺ T cells is likely balanced by continuous proliferation of these cells in attempts to maintain this threshold. Further evidence for this model comes from studies demonstrating that macaques that fail to maintain proliferation of memory CD4⁺ T cells rapidly progress to AIDS (Picker et al. 2004).

Antiretroviral Therapy and the Mucosal Immune System

The potential for antiretroviral therapy (ART) to restore mucosal CD4⁺ T cells has only begun to be examined and has been particularly difficult to assess in acute infection. Small studies in

A.A. Lackner et al.

humans and SIV-infected macaques have suggested near-complete restoration of mucosal CD4⁺ T cells when treatment is initiated very early (George et al. 2005; Guadalupe et al. 2006). In contrast, other studies have not shown a significant restoration of mucosal CD4⁺ T cells either early or late in infection (Anton et al. 2003; Mehandru et al. 2006; Poles et al. 2006), whereas still other studies have shown significant restoration of CD4⁺ T cells including the Th17 subset (Macal et al. 2008). In summary, although CD4⁺ T-cell numbers in the peripheral blood often fully reconstitute in patients on ART, there is considerable controversy regarding the capacity of ART to restore intestinal CD4⁺ T cells. Furthermore, even after suppression of detectable plasma viremia by ART, HIV can be detected and recovered in the intestinal mucosa and other tissues (Anton et al. 2003; Mehandru et al. 2006; Poles et al. 2006; Belmonte et al. 2007; Chun et al. 2008). Persistent viral replication in the intestine of SIV-infected long-term nonprogressing macaques with undetectable viremia has also been described (Ling et al. 2004). These data suggest that the intestinal immune system is an important reservoir of SIV/HIV infection and that ongoing viral replication occurs in the intestine of patients on ART, despite what appears to be nearly complete suppression of viral levels in the blood. Thus, a major challenge for antiretroviral control of HIV infection appears to be in mucosal tissues, particularly the intestine.

NEW RESEARCH AREAS

The Role of Immune Activation in HIV and SIV Disease Pathogenesis

Despite profound immune deficiency, there is evidence of profound immune activation in HIV infection. T lymphocytes, B lymphocytes, and antigen-presenting cells of the innate immune system have phenotypic and functional evidence of activation. Hyperglobulinemia and increased circulating levels of proinflammatory cytokines are characteristic, and although type 1 interferon levels are often difficult to measure in circulation, transcriptional analyses indicate

that HIV infection is associated with profound activation of interferon-responsive genes (Woelk et al. 2004; Hyrcza et al. 2007). T lymphocytes often express high levels of activation markers such as CD38 and HLA-DR (Giorgi et al. 1993). Markers of immune senescence such as CD57 (Brenchley et al. 2003) and immune exhaustion such as programmed death receptor type 1 (PD-1) (Day et al. 2006; Trautmann et al. 2006) are elevated, and cells expressing each of these markers have demonstrable impairments in response to TCR stimulation. Markers of immune activation are recognized predictors of disease outcome in HIV infection (Giorgi et al. 1993, 1999; Liu et al. 1997, 1998; Hazenberg et al. 2003; Deeks et al. 2004; Wilson et al. 2004). Expression of the activation marker CD38 on T cells is a valuable predictor of disease outcome in HIV infection (Giorgi et al. 1993, 1999; Liu et al. 1997). Likewise, plasma levels of IL-6, TNF receptors and markers of coagulation (d-dimer levels) predict mortality in treated HIV infection (Kuller et al. 2008; Kalayjian et al. 2010). One of the hallmarks of immune activation in HIV infection is a marked increase in T-cell turnover, as measured by incorporation of bromodeoxyuridine or deuterated glucose and expression of the nuclear antigen Ki-67, which indicates cell cycling (Sachsenberg et al. 1998; Douek et al. 2001; Kovacs et al. 2001; Mohri et al. 2001). This increase in cycling is seen in both CD4 and CD8 T-cell populations (Kovacs et al. 2001) and is especially striking among central memory cells in both humans and in SIV-infected macaques (Picker et al. 2004; Sieg et al. 2005). Activated cycling CD4⁺ T cells are both more susceptible to productive HIV infection (Zack et al. 1990; Ramilo et al. 1993) and also tend to die *ex vivo*, likely as a result of programmed cell death (Sieg et al. 2008).

In nonhuman primate models of SIV infection, immune activation and inflammation distinguish the pathogenic models of SIV infection in rhesus macaques from the nonpathogenic outcomes of SIV infection in naturally adapted hosts that tolerate SIV replication typically with no or minimal losses of circulating CD4 T cells (Chakrabarti et al. 2000; Silvestri et al. 2003).

Several potential drivers have been postulated to account for this state of systemic immune activation in progressive HIV and SIV infection. Among these is the virus itself, which can drive activation of innate immune receptors such as TLR 7 and 8 through poly(U)-rich sequences in its genome (Beignon et al. 2005; Meier et al. 2007) as well as possibly through activation of other innate immune receptors by capsid proteins (Manel et al. 2010) or viral DNAs (Yan et al. 2010). A rapid decrease in immune activation indices is recognized with administration of suppressive antiviral drugs and it is likely that some of this decrease is a consequence of lower levels of HIV replication (Evans et al. 1998; Tilling et al. 2002). Some level of T-cell activation in HIV infection also may be mediated directly through recognition of peptides by TCRs. These peptides may be derived from HIV itself but also from opportunistic microbes (such as cytomegalovirus and other herpes viruses) that have been permitted to replicate more effectively in the setting of HIV-related immune deficiency (Hunt et al. 2011). It is also possible that some level of immune activation in HIV and pathogenic SIV infection is related to homeostatic mechanisms, that is, a need to replenish lymphocyte populations at effector sites of potential microbial invasion (Okoye et al. 2007). Finally, there is increasing evidence that in HIV and in pathogenic SIV infection, early damage to mucosal CD4⁺ T-cell defenses permits increased translocation of microbial products from the gut to the systemic circulation (Brenchley et al. 2006) and these microbial products can drive T-cell and innate immune cell activation (Brenchley et al. 2006; Funderburg et al. 2008). These mechanisms are summarized in Figure 1.

Understanding Microbial Translocation

The human gastrointestinal mucosal surface comprises an estimated surface area of >2700 square feet designed to promote absorption of needed nutrients and fluids and to contain within the lumen the dense population of colonizing microbes and their products. Yet even in healthy subjects, microbial products such as the

lipopolysaccharide components of bacterial cell walls can be found in circulation (Brenchley et al. 2006). During acute HIV infection in humans and SIV infection in both African naturally adapted hosts for SIV infection and Asian macaques that develop AIDS, there is a dramatic loss of mucosal CD4⁺ CCR5⁺ T cells that are critical targets for productive HIV and SIV infection (Veazey et al. 1998; Brenchley et al. 2004b). In both humans and rhesus, this is followed by an apparent breakdown in the mucosal barrier to systemic translocation of microbial products (Fig 2). Thus, in these systems, high levels of bacterial products can be found in circulation and this microbial translocation is linked to indices of immune activation. The precise mechanisms of the loss of barrier function are incompletely understood but epithelial damage (Estes et al. 2010) and relatively selective losses of Th17 CD4 cells at mucosal sites (Ferreira et al. 1990; Brenchley et al. 2008; Macal et al. 2008; Raffatellu et al. 2008) have been shown. How microbial translocation affects immune homeostasis and HIV pathogenesis is unproven, but in vitro, these microbial products can activate human T cells (Funderburg et al. 2008), and in vivo, indices of microbial translocation activation are linked both to a more aggressive course of HIV infection (Sandler et al. 2011) and inversely to the magnitude of CD4 T-cell restoration with antiviral therapy (Fig. 1) (Brenchley et al. 2006; Jiang et al. 2009). Correlation of course does not prove causality and interventional studies will be required to ascertain if a causal relationship among microbial translocation, immune activation, and HIV pathogenesis exists.

A number of strategies are in development in an effort to preserve mucosal integrity, to limit or prevent microbial translocation in HIV infection, and to test the hypothesis that microbial translocation is an important contributor to both immune activation and HIV pathogenesis. Although data are limited, there is evidence that suppressive antiretroviral therapy is associated with both improvement in mucosal integrity (Guadalupe et al. 2006; Macal et al. 2008; Sheth et al. 2008; Epple et al. 2009) and reduction in the microbial translocation that is its

A.A. Lackner et al.

Figure 1. Drivers of immune activation and cellular turnover in HIV infection. In progressive HIV and SIV infection, increased immune activation and accelerated cellular turnover are thought to play a central role in T-cell depletion and immune suppression. Whereas HIV can contribute directly to immune activation, both through TLR signaling and direct antigenic stimulation of T cells (*top center*), much of the uncontrolled immune activation is thought to occur via non-HIV-specific mechanisms. Microbial products such as lipopolysaccharide derived from intestinal bacteria enter the systemic circulation in increased quantities, owing to damage to the mucosal immune system and the integrity of the epithelial barrier function, and stimulate innate immune cells through pathogen-associated molecular pattern recognition receptors, which in turn activate adaptive T cells through proinflammatory cytokine expression (*bottom and center right*). Other viruses, including cytomegalovirus (CMV) and other human herpes viruses, which are more prevalent in HIV infection, are emerging as potential contributors to this process as well (*bottom center*). As T cells become depleted, decreasing numbers trigger homeostatic mechanisms that further drive existing cells into cycle and potentially contribute to further depletion as HIV infection preferentially infects and destroys activated CD4⁺ T cells (*left*).

presumed consequence (Brenchley et al. 2006). Several targeted interventions have been designed in an effort to block systemic translocation of microbial products in HIV disease. Oral administration of bovine colostrum prepared from cows immunized with *Escherichia coli* has been tested in two clinical trials with either no effect (Purcell et al. 2011) or very modest effects on indices of immune activation (Yadavalli et al.

2011). Sevalemer is a phosphate-binding resin that also binds lipopolysaccharide (LPS) and its administration to patients with renal insufficiency has been associated with decreased plasma LPS levels. An ongoing trial in HIV infection (ACTG 5296) will test the effects of intraluminal binding of LPS by sevalemer on immune activation and CD4 T-cell homeostasis. In SIV-infected rhesus macaques, administration

Figure 2. The intestinal immune system in HIV infection. Within days after initial HIV or SIV infection, and regardless of the route of acquisition, terminally differentiated memory $CD4^{+} CCR5^{+}$ T cells in the intestinal submucosa are massively depleted, as they are preferentially targeted by HIV (1). Th17 T cells, which play a crucial role in maintaining the integrity of the mucosa and defending against luminal pathogens, are especially depleted (2), further diminishing the effectiveness of the epithelial barrier function. Additionally, tight junctions among epithelial cells are damaged and enterocytes undergo apoptosis, resulting in physical breaches of epithelial integrity, which facilitate systemic exposure to luminal pathogens (3). Antiretroviral therapy appears to correct these defects only to a minimal extent, and the resulting, ongoing exposure to microbial-derived products is thought to be partly responsible for the persistent immune activation, inflammation, and adverse events seen even in HIV-infected persons who have achieved maximal suppression of viral replication.

of antibacterial agents was associated with only transient decreases in plasma LPS levels (Brenchley et al. 2006). Nonetheless, a trial of oral administration of the nonabsorbable antibiotic rifaximin is under way in persons with chronic HIV infection (ACTG 5286).

Moving downstream, the antimalarial drugs chloroquine and hydroxychloroquine have the capability of blocking signaling after ligation of toll-like receptors (Martinson et al. 2010). In one small trial, chloroquine administration to persons with chronic HIV infection decreased indices of immune activation (CD38 and HLA-DR) on CD8 but not CD4 T cells (Murray et al. 2010). In another single-arm study, administration of hydroxychloroquine to HIV-infected persons who experienced suboptimal CD4 T-cell

gains after highly active antiretroviral therapy (HAART) resulted in decreased levels of T-cell activation and decreased levels of inflammatory cytokines IL-6 and TNF in plasma (Piconi et al. 2011). Thus, there is some indication that activation of the toll-like receptor signaling pathway plays some role in the immune activation and inflammation that characterize HIV infection.

The Role of Inflammation/Activation in the Complications of Treated HIV Infection

With widespread use of HAART, deaths attributed to AIDS have diminished rapidly (Palella et al. 2006) and in the HAART era, major AIDS-defining opportunistic infections are no longer the major cause of mortality. Instead, cardiovas-

A.A. Lackner et al.

cular disease, liver disease, and a broadening spectrum of malignancies appear to comprise the major causes of morbidity and death in HIV-infected persons, particularly in the setting of late initiation of antiretroviral therapy (Lau et al. 2007; Marin et al. 2009; Mocroft et al. 2010). These events appear to be more common in HIV-infected persons than among the general population (Weber et al. 2006; Choi et al. 2007; Kirk et al. 2007; Triant et al. 2007; Engels et al. 2008; Joshi et al. 2011) and overall, the risk of these events appears greater in patients with lower circulating CD4⁺ T-cell counts (Weber et al. 2005; Baker et al. 2008). The determinants of these outcomes are not entirely clear; however, several large studies have linked mortalities in the HAART era to plasma makers of inflammation and coagulation (Kuller et al. 2008; Kalayjian et al. 2010). In a very large study of intermittent versus continuous antiretroviral therapy (the SMART study), plasma levels of IL-6, C-reactive protein,

and d-dimer products of thrombolysis independently predicted mortality and cardiovascular morbidities (El-Sadr et al. 2006; Kuller et al. 2008). What is driving these inflammatory and coagulation markers is not entirely clear, but in a nested case-control substudy of SMART, plasma levels of the LPS receptor (sCD14) independently predicted mortality (Sandler et al. 2011). It is likely that HIV replication plays an important role in immune activation and inflammation, as both immune activation indices and plasma inflammatory markers are elevated in untreated infection and diminish after suppressive antiretroviral therapies (Evans et al. 1998; Tilling et al. 2002). On the other hand, some persons who initiate antiretroviral therapies late in the course of disease are unable to raise their circulating CD4 T-cell counts to “normal” levels despite apparent complete suppression of HIV replication (Kelley et al. 2009). The determinants of immune failure in this setting are incompletely understood but what has

Figure 3. Activation of adaptive and innate immune mechanisms drives HIV pathogenesis in lymphoid tissue. HIV replication within lymphoid tissue promotes an increased local accumulation of HIV-reactive effector (E) T cells that are activated and expanded as a result of exposure to HIV peptides. HIV also activates antigen-presenting cells (APC)—monocytes/macrophages and dendritic cells via ligation of innate immune receptors to express inflammatory cytokines. This proinflammatory environment promotes more effector cell sequestration and also drives central memory (CM) T cells into cell cycle. Inflammation drives collagen deposition and progressive fibrosis, hindering intercellular communications and access to IL-7 that is necessary for homeostatic T-cell expansion. With further translocation of microbial products from the damaged gut, more APC are activated through innate receptors to induce a proinflammatory and procoagulant state that may underlie the increased cardiovascular risk seen in HIV infection.

been described as “fibrosis” of lymphoid tissues is associated with failure of CD4 T-cell restoration on HAART (Fig. 3) (Schacker et al. 2002, 2005). Interestingly, in these incomplete immune responders, immune activation indices are elevated as are plasma inflammatory and coagulation markers (Hunt et al. 2008; Marchetti et al. 2008; Shive et al. 2011). Markers of microbial translocation tend to be elevated in these subjects (Hunt et al. 2008; Marchetti et al. 2008; Shive et al. 2011) and the profile of T-cell activation and cycling is similar to the profile seen after in vitro exposure to microbial products (Funderburg et al. 2008; Lederman et al. 2010).

CONCLUSIONS

It is now clear that HIV and SIV prefer to infect activated memory CD4⁺ T cells that express CCR5 and that most of the T cells of this phenotype reside in the intestine and other mucosal sites. The recognition that progressive HIV and SIV infection is linked to immune activation, which in turn is linked to a leaky gut, has only recently focused intense interest on the effects of HIV and SIV infection on the intestinal epithelial barrier. The details of how infection and loss of intestinal CD4⁺ T cells leads to a “leaky gut” are unclear, but multiple avenues of investigation have begun to be explored. If it were possible to prevent or decrease the breakdown of the mucosal barrier through therapeutic means, it is possible that this could greatly slow AIDS disease progression, as appears to be the case in natural nonhuman primate hosts of SIV that are persistently infected, suffer acute loss of intestinal CD4⁺ T cells, but apparently do not have a leaky gut nor chronic immune activation and rarely progress to AIDS.

REFERENCES

- Abel K, Rocke DM, Chohan B, Fritts L, Miller CJ. 2005. Temporal and anatomic relationship between virus replication and cytokine gene expression after vaginal simian immunodeficiency virus infection. *J Virol* **79**: 12164–12172.
- Alkhatib G, Combadiere C, Broder CC, Feng Y, Kennedy PE, Murphy PM, Berger EA. 1996. CC CKR5: A RANTES, MIP-1a, MIP-1b receptor as a fusion cofactor for macrophage-tropic HIV-1. *Science* **272**: 1955–1958.
- Antiretroviral Therapy Cohort Collaboration. 2008. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: A collaborative analysis of 14 cohort studies. *Lancet* **372**: 293–299.
- Anton PA, Mitsuyasu RT, Deeks SG, Scadden DT, Wagner B, Huang C, Macken C, Richman DD, Christopherson C, Borellini F, et al. 2003. Multiple measures of HIV burden in blood and tissue are correlated with each other but not with clinical parameters in aviremic subjects. *AIDS* **17**: 53–63.
- Apetrei C, Kaur A, Lerche NW, Metzger M, Pandrea I, Hardcastle J, Falkenstein S, Bohm R, Koehler J, Traina-Dorge V, et al. 2005. Molecular epidemiology of simian immunodeficiency virus SIVsm in U.S. primate centers unravels the origin of SIVmac and SIVstm. *J Virol* **79**: 8991–9005.
- Arron ST, Ribeiro RM, Gettie A, Bohm R, Blanchard J, Yu J, Perelson AS, Ho DD, Zhang L. 2005. Impact of thymectomy on the peripheral T cell pool in rhesus macaques before and after infection with simian immunodeficiency virus. *Eur J Immunol* **35**: 46–55.
- Asquith B, Edwards CT, Lipsitch M, McLean AR. 2006. Inefficient cytotoxic T lymphocyte-mediated killing of HIV-1-infected cells in vivo. *PLoS Biol* **4**: e90. doi: 10.1371/journal.pbio.0040090.
- Autran B, Carcelain G, Li TS, Blanc C, Mathez D, Tubiana R, Katlama C, Debre P, Leibowitch J. 1997. Positive effects of combined antiretroviral therapy on CD4⁺ T cell homeostasis and function in advanced HIV disease. *Science* **277**: 112–116.
- Baggaley RF, White RG, Boily MC. 2008. Systematic review of orogenital HIV-1 transmission probabilities. *Int J Epidemiol* **37**: 1255–1265.
- Bailey JR, Lassen KG, Yang HC, Quinn TC, Ray SC, Blankson JN, Siliciano RE. 2006. Neutralizing antibodies do not mediate suppression of human immunodeficiency virus type 1 in elite suppressors or selection of plasma virus variants in patients on highly active antiretroviral therapy. *J Virol* **80**: 4758–4770.
- Baker JV, Peng G, Rapkin J, Abrams DI, Silverberg MJ, MacArthur RD, Cavert WP, Henry WK, Neaton JD. 2008. CD4⁺ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS* **22**: 841–848.
- Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dautet C, Axler-Blin C, Vezinet-Brun F, Rouzioux C, et al. 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science* **220**: 868–871.
- Batman PA, Miller AR, Forster SM, Harris JR, Pinching AJ, Griffin GE. 1989. Jejunal enteropathy associated with human immunodeficiency virus infection: Quantitative histology. *J Clin Pathol* **42**: 275–281.
- Beignon AS, McKenna K, Skoberne M, Manches O, DaSilva I, Kavanagh DG, Larsson M, Gorelick RJ, Lifson JD, Bhardwaj N. 2005. Endocytosis of HIV-1 activates plasmacytoid dendritic cells via Toll-like receptor-viral RNA interactions. *J Clin Invest* **115**: 3265–3275.
- Belmonte L, Olmos M, Fanin A, Parodi C, Bare P, Concetti H, Perez H, de Bracco MM, Cahn P. 2007. The intestinal

A.A. Lackner et al.

- mucosa as a reservoir of HIV-1 infection after successful HAART. *AIDS* **21**: 2106–2108.
- Betts MR, Ambrozak DR, Douek DC, Bonhoeffer S, Brenchley JM, Casazza JP, Koup RA, Picker LJ. 2001. Analysis of total human immunodeficiency virus (HIV)-specific CD4⁺ and CD8⁺ T-cell responses: Relationship to viral load in untreated HIV infection. *J Virol* **75**: 11983–11991.
- Betts MR, Nason MC, West SM, De Rosa SC, Migueles SA, Abraham J, Lederman MM, Benito JM, Goepfert PA, Connors M, et al. 2006. HIV nonprogressors preferentially maintain highly functional HIV-specific CD8⁺ T cells. *Blood* **107**: 4781–4789.
- Blankson JN, Bailey JR, Thayil S, Yang HC, Lassen K, Lai J, Gandhi SK, Siliciano JD, Williams TM, Siliciano RF. 2007. Isolation and characterization of replication-competent human immunodeficiency virus type 1 from a subset of elite suppressors. *J Virol* **81**: 2508–2518.
- Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, Alary M. 2009. Heterosexual risk of HIV-1 infection per sexual act: Systematic review and meta-analysis of observational studies. *Lancet Infect Dis* **9**: 118–129.
- Brenchley JM, Karandikar NJ, Betts MR, Ambrozak DR, Hill BJ, Crotty LE, Casazza JP, Kuruppu J, Migueles SA, Connors M, et al. 2003. Expression of CD57 defines replicative senescence and antigen-induced apoptotic death of CD8⁺ T cells. *Blood* **101**: 2711–2720.
- Brenchley JM, Hill BJ, Ambrozak DR, Price DA, Guenaga FJ, Casazza JP, Kuruppu J, Yazdani J, Migueles SA, Connors M, et al. 2004a. T-cell subsets that harbor human immunodeficiency virus (HIV) in vivo: Implications for HIV pathogenesis. *J Virol* **78**: 1160–1168.
- Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, Nguyen PL, Khoruts A, Larson M, Haase AT, et al. 2004b. CD4⁺ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med* **200**: 749–759.
- Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte O, Altmann D, et al. 2006. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* **12**: 1365–1371.
- Brenchley JM, Paiardini M, Knox KS, Asher AI, Cervasi B, Asher TE, Scheinberg P, Price DA, Hage CA, Kholi LM, et al. 2008. Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections. *Blood* **112**: 2826–2835.
- Carrington M, Nelson GW, Martin MP, Kissner T, Vlahov D, Goedert JJ, Kaslow R, Buchbinder S, Hoots K, O'Brien SJ. 1999. HLA and HIV-1: Heterozygote advantage and B*35-Cw*04 disadvantage. *Science* **283**: 1748–1752.
- Chakrabarti LA, Lewin SR, Zhang L, Gettie A, Luckay A, Martin LN, Skulsky E, Ho DD, Cheng-Mayer C, Marx PA. 2000. Normal T-cell turnover in sooty mangabeys harboring active simian immunodeficiency virus infection. *J Virol* **74**: 1209–1223.
- Choi AI, Rodriguez RA, Bacchetti P, Bertenthal D, Volberding PA, O'Hare AM. 2007. Racial differences in end-stage renal disease rates in HIV infection versus diabetes. *J Am Soc Nephrol* **18**: 2968–2974.
- Chou CS, Ramilo O, Vitetta ES. 1997. Highly purified CD25-resting T cells cannot be infected de novo with HIV-1. *Proc Natl Acad Sci* **94**: 1361–1365.
- Chun TW, Nickle DC, Justement JS, Meyers JH, Roby G, Hallahan CW, Kottlil S, Moir S, Mican JM, Mullins JI, et al. 2008. Persistence of HIV in gut-associated lymphoid tissue despite long-term antiretroviral therapy. *J Infect Dis* **197**: 714–720.
- Clayburgh DR, Shen L, Turner JR. 2004. A porous defense: The leaky epithelial barrier in intestinal disease. *Lab Invest* **84**: 282–291.
- Cummins AG, LaBrooy JT, Stanley DP, Rowland R, Shearman DJ. 1990. Quantitative histological study of enteropathy associated with HIV infection. *Gut* **31**: 317–321.
- Day CL, Kaufmann DE, Kiepiela P, Brown JA, Moodley ES, Reddy S, Mackey EW, Miller JD, Leslie AJ, DePierres C, et al. 2006. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature* **443**: 350–354.
- Deacon NJ, Tsykin A, Solomon A, Smith K, Ludford-Menting M, Hooker DJ, McPhee DA, Greenway AL, Ellett A, Chatfield C, et al. 1995. Genomic structure of an attenuated quasi species of HIV-1 from a blood transfusion donor and recipients. *Science* **270**: 988–991.
- Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, Goedert JJ, Buchbinder SP, Vittinghoff E, Gomperts E, et al. 1996. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. *Science* **273**: 1856–1862.
- Deeks SG, Kitchen CM, Liu L, Guo H, Gascon R, Narvaez AB, Hunt P, Martin JN, Kahn JO, Levy J, et al. 2004. Immune activation set point during early HIV infection predicts subsequent CD4⁺ T-cell changes independent of viral load. *Blood* **104**: 942–947.
- Dion ML, Bordin R, Zeidan J, Asaad R, Boulassel MR, Routy JP, Lederman MM, Sekaly RP, Cheynier R. 2007. Slow disease progression and robust therapy-mediated CD4⁺ T-cell recovery are associated with efficient thymopoiesis during HIV-1 infection. *Blood* **109**: 2912–2920.
- Doitsh G, Cavois M, Lassen KG, Zepeda O, Yang Z, Santiago ML, Hebbeler AM, Greene WC. 2010. Abortive HIV infection mediates CD4 T cell depletion and inflammation in human lymphoid tissue. *Cell* **143**: 789–801.
- Douek DC, McFarland RD, Keiser PH, Gage EA, Massey JM, Haynes BF, Polis MA, Haase AT, Feinberg MB, Sullivan JL, et al. 1998. Changes in thymic function with age and during the treatment of HIV infection. *Nature* **396**: 690–695.
- Douek DC, Betts MR, Hill BJ, Little SJ, Lempicki R, Metcalf JA, Casazza J, Yoder C, Adelsberger JW, Stevens RA, et al. 2001. Evidence for increased T cell turnover and decreased thymic output in HIV infection. *J Immunol* **167**: 6663–6668.
- Douek DC, Brenchley JM, Betts MR, Ambrozak DR, Hill BJ, Okamoto Y, Casazza JP, Kuruppu J, Kunstman K, Wolinsky S, et al. 2002. HIV preferentially infects HIV-specific CD4⁺ T cells. *Nature* **417**: 95–98.
- El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, Babiker A, Burman W, Clumeck N, Cohen

- CJ, et al. 2006. CD4⁺ count-guided interruption of antiretroviral treatment. *N Engl J Med* **355**: 2283–2296.
- Emu B, Sinclair E, Hatano H, Ferre A, Shacklett B, Martin JN, McCune JM, Deeks SG. 2008. HLA class I-restricted T-cell responses may contribute to the control of human immunodeficiency virus infection, but such responses are not always necessary for long-term virus control. *J Virol* **82**: 5398–5407.
- Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, Grigg R, Hylton T, Pawlish KS, McNeel TS, et al. 2008. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* **123**: 187–194.
- Eppl HJ, Schneider T, Troeger H, Kunkel D, Allers K, Moos V, Amasheh M, Loddenkemper C, Fromm M, Zeitl M, et al. 2009. Impairment of the intestinal barrier is evident in untreated but absent in suppressively treated HIV-infected patients. *Gut* **58**: 220–227.
- Estes JD, Harris LD, Klatt NR, Tabb B, Pittaluga S, Paiardini M, Barclay GR, Smedley J, Pung R, Oliveira KM, et al. 2010. Damaged intestinal epithelial integrity linked to microbial translocation in pathogenic simian immunodeficiency virus infections. *PLoS Pathog* **6**: e1001052. doi: 10.1371/journal.ppat.1001052.
- Evans TG, Bonnez W, Soucier HR, Fitzgerald T, Gibbons DC, Reichman RC. 1998. Highly active antiretroviral therapy results in a decrease in CD8⁺ T cell activation and preferential reconstitution of the peripheral CD4⁺ T cell population with memory rather than naive cells. *Antiviral Res* **39**: 163–173.
- Favre D, Lederer S, Kanwar B, Ma ZM, Proll S, Kasakow Z, Mold J, Swainson L, Barbour JD, Baskin CR, et al. 2009. Critical loss of the balance between Th17 and Tregulatory cell populations in pathogenic SIV infection. *PLoS Pathog* **5**: e1000295. doi: 10.1371/journal.ppat.1000295.
- Ferreira RC, Forsyth LE, Richman PI, Wells C, Spencer J, MacDonald TT. 1990. Changes in the rate of crypt epithelial cell proliferation and mucosal morphology induced by a T-cell-mediated response in human small intestine. *Gastroenterol* **98**: 1255–1263.
- Field M. 2006. T cell activation alters intestinal structure and function. *J Clin Invest* **116**: 2580–2582.
- Funderburg N, Luciano AA, Jiang W, Rodriguez B, Sieg SE, Lederman MM. 2008. Toll-like receptor ligands induce human T cell activation and death, a model for HIV pathogenesis. *PLoS One* **3**: e1915. doi: 10.1371/journal.pone.0001915.
- Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, Palker TJ, Redfield R, Oleske J, Safai B, et al. 1984. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* **224**: 500–503.
- Gao F, Yue L, White AT, Pappas PG, Barchue J, Hanson AP, Greene BM, Sharp PM, Shaw GM, Hahn BH. 1992. Human infection by genetically diverse SIVSM-related HIV-2 in west Africa. *Nature* **358**: 495–499.
- Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, Michael SE, Cummins LB, Arthur LO, Peeters M, Shaw GM, et al. 1999. Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. *Nature* **397**: 436–441.
- George MD, Reay E, Sankaran S, Dandekar S. 2005. Early antiretroviral therapy for simian immunodeficiency virus infection leads to mucosal CD4⁺ T-cell restoration and enhanced gene expression regulating mucosal repair and regeneration. *J Virol* **79**: 2709–2719.
- George MD, Wehkamp J, Kays RJ, Leutenegger CM, Sabir S, Grishina I, Dandekar S, Bevins CL. 2008. In vivo gene expression profiling of human intestinal epithelial cells: Analysis by laser microdissection of formalin fixed tissues. *BMC Genomics* **9**: 209.
- Giorgi JV, Liu Z, Hultin LE, Cumberland WG, Hennessey K, Detels R. 1993. Elevated levels of CD38⁺ CD8⁺ T cells in HIV infection add to the prognostic value of low CD4⁺ T cell levels: Results of 6 years of follow-up. The Los Angeles Center, Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr* **6**: 904–912.
- Giorgi JV, Hultin LE, McKeating JA, Johnson TD, Owens B, Jacobson LP, Shih R, Lewis J, Wiley DJ, Phair JP, et al. 1999. Shorter survival in advanced human immunodeficiency virus type 1 infection is more closely associated with T lymphocyte activation than with plasma virus burden or virus chemokine coreceptor usage. *J Infect Dis* **179**: 859–870.
- Goedert JJ, Biggar RJ, Weiss SH, Eyster ME, Melbye M, Wilson S, Ginzburg HM, Grossman RJ, DiGioia RA, Sanchez WC, et al. 1986. Three-year incidence of AIDS in five cohorts of HTLV-III-infected risk group members. *Science* **231**: 992–995.
- Gonzalez-Scarano F, Martin-Garcia J. 2005. The neuro-pathogenesis of AIDS. *Nat Rev Immunol* **5**: 69–81.
- Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A. 1981. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: Evidence of a new acquired cellular immunodeficiency. *N Engl J Med* **305**: 1425–1431.
- Goulder PJ, Bunce M, Krausa B, McIntyre K, Crowley S, Morgan B, Edwards A, Giangrande P, Phillips RE, McMichael AJ. 1996. Novel, cross-restricted, conserved, and immunodominant cytotoxic T lymphocyte epitopes in slow progressors in HIV type 1 infection. *AIDS Res Hum Retrov* **12**: 1691–1698.
- Grossman Z, Meier-Schellersheim M, Paul WE, Picker LJ. 2006. Pathogenesis of HIV infection: What the virus spares is as important as what it destroys. *Nat Med* **12**: 289–295.
- Guadalupe M, Sankaran S, George MD, Reay E, Verhoeven D, Shacklett BL, Flamm J, Wegelin J, Prindiville T, Dandekar S. 2006. Viral suppression and immune restoration in the gastrointestinal mucosa of human immunodeficiency virus type 1-infected patients initiating therapy during primary or chronic infection. *J Virol* **80**: 8236–8247.
- Haase AT, Henry K, Zupancic M, Sedgewick G, Faust RA, Melroe H, Cavert W, Gebhard K, Staskus K, Zhang Z-Q, et al. 1996. Quantitative image analysis of HIV-1 infection in lymphoid tissue. *Science* **274**: 985–989.
- Harcourt G, Gomperts E, Donfield S, Klenerman P. 2006. Diminished frequency of hepatitis C virus specific interferon gamma secreting CD4⁺ T cells in human immunodeficiency virus/hepatitis C virus coinfecting patients. *Gut* **55**: 1484–1487.

A.A. Lackner et al.

- Hasegawa A, Liu H, Ling B, Borda JT, Alvarez X, Sugimoto C, Vinet-Oliphant H, Kim WK, Williams KC, Ribeiro RM, et al. 2009. The level of monocyte turnover predicts disease progression in the macaque model of AIDS. *Blood* **114**: 2917–2925.
- Hasse B, Ledergerber B, Egger M, Vernazza P, Furrer H, Battegay M, Hirschel B, Cavassini M, Bernasconi E, Weber R. 2011. Aging and (non-HIV-associated) co-morbidity in HIV-positive persons: The Swiss HIV cohort study (SHCS). In *18th Conference on Retroviruses and Opportunistic Infections, Abstract O-161*. Boston.
- Haynes BE, Hale LB, Weinhold KJ, Patel DD, Liao HX, Bressler PB, Jones DM, Demarest JE, Gebhard-Mitchell K, Haase AT, et al. 1999. Analysis of the adult thymus in reconstitution of T lymphocytes in HIV-1 infection. *J Clin Invest* **103**: 453–460.
- Hazenber MD, Otto SA, van Benthem BH, Roos MT, Coutinho RA, Lange JM, Hamann D, Prins M, Miedema E. 2003. Persistent immune activation in HIV-1 infection is associated with progression to AIDS. *AIDS* **17**: 1881–1888.
- Heise C, Vogel P, Miller CJ, Halsted CH, Dandekar S. 1993. Simian immunodeficiency virus infection of the gastrointestinal tract of rhesus macaques: Functional, pathological and morphological changes. *Am J Pathol* **142**: 1759–1771.
- Heise C, Miller CJ, Lackner A, Dandekar S. 1994. Primary acute simian immunodeficiency virus infection of intestinal lymphoid tissue is associated with gastrointestinal dysfunction. *J Infect Dis* **169**: 1116–1120.
- Hirschtick RE, Glassroth J, Jordan MC, Wilcosky TC, Wallace JM, Kvale PA, Markowitz N, Rosen MJ, Mangura BT, Hopewell PC. 1995. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med* **333**: 845–851.
- Horton H, Vogel T, O'Connor D, Picker L, Watkins DI. 2002. Analysis of the immune response and viral evolution during the acute phase of SIV infection. *Vaccine* **20**: 1927–1932.
- Hu JJ, Gardner MB, Miller CJ. 2000. Simian immunodeficiency virus rapidly penetrates the cervicovaginal mucosa after intravaginal inoculation and infects intraepithelial dendritic cells. *J Virol* **74**: 6087–6095.
- Hunt PW, Brenchley J, Sinclair E, McCune JM, Roland M, Page-Shafer K, Hsue P, Emu B, Krone M, Lampiris H, et al. 2008. Relationship between T cell activation and CD4⁺ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. *J Infect Dis* **197**: 126–133.
- Hunt P, Martin J, Sinclair E, Epling L, Teague J, Jacobson M, Tracy R, Corey L, Deeks SG. 2011. Valganciclovir reduces T cell activation in HIV-infected individuals with incomplete CD4⁺ T cell recovery on antiretroviral therapy. *J Infect Dis* **203**: 1474–1483.
- Hyrca MD, Kovacs C, Loutfy M, Halpenny R, Heisler L, Yang S, Wilkins O, Ostrowski M, Der SD. 2007. Distinct transcriptional profiles in ex vivo CD4⁺ and CD8⁺ T cells are established early in human immunodeficiency virus type 1 infection and are characterized by a chronic interferon response as well as extensive transcriptional changes in CD8⁺ T cells. *J Virol* **81**: 3477–3486.
- Ioannidis JP, Rosenberg PS, Goedert JJ, Ashton LJ, Benfield TL, Buchbinder SP, Coutinho RA, Eugen-Olsen J, Gallart T, Katzenstein TL, et al. 2001. Effects of CCR5-Δ32, CCR2-64I, and SDF-1 3'A alleles on HIV-1 disease progression: An international meta-analysis of individual-patient data. *Ann Intern Med* **135**: 782–795.
- James SP, Graeff AS, Zeitz M. 1987. Predominance of helper-inducer T cells in mesenteric lymph nodes and intestinal lamina propria of normal nonhuman primates. *Cell Immunol* **107**: 372–383.
- Janoff EN, Breiman RF, Daley CL, Hopewell PC. 1992. Pneumococcal disease during HIV infection. Epidemiologic, clinical, and immunologic perspectives. *Ann Intern Med* **117**: 314–324.
- Jiang W, Lederman MM, Hunt P, Sieg SF, Haley K, Rodriguez B, Landay A, Martin J, Sinclair E, Asher AI, et al. 2009. Plasma levels of bacterial DNA correlate with immune activation and the magnitude of immune restoration in persons with antiretroviral-treated HIV infection. *J Infect Dis* **199**: 1177–1185.
- Joshi D, O'Grady J, Dieterich D, Gazzard B, Agarwal K. 2011. Increasing burden of liver disease in patients with HIV infection. *Lancet* **377**: 1198–1209.
- Kalayjian RC, Machekano RN, Rizk N, Robbins GK, Gandhi RT, Rodriguez BA, Pollard RB, Lederman MM, Landay A. 2010. Pretreatment levels of soluble cellular receptors and interleukin-6 are associated with HIV disease progression in subjects treated with highly active antiretroviral therapy. *J Infect Dis* **201**: 1796–1805.
- Kaslow RA, Duquesnoy R, VanRaden M, Kingsley L, Marrari M, Friedman H, Su S, Saah AJ, Detels R, Phair J, et al. 1990. A1, Cw7, B8, DR3 HLA antigen combination associated with rapid decline of T-helper lymphocytes in HIV-1 infection. A report from the Multicenter AIDS Cohort Study. *Lancet* **335**: 927–930.
- Kaslow RA, Carrington M, Apple R, Park L, Munoz A, Saah AJ, Goedert JJ, Winkler C, O'Brien SJ, Rinaldo C, et al. 1996. Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. *Nat Med* **2**: 405–411.
- Kaur A, Hale CL, Ramanujan S, Jain RK, Johnson RP. 2000. Differential dynamics of CD4⁺ and CD8⁺ T-lymphocyte proliferation and activation in acute simian immunodeficiency virus infection. *J Virol* **74**: 8413–8424.
- Kelley CE, Kitchen CM, Hunt PW, Rodriguez B, Hecht FM, Kitahata M, Crane HM, Willig J, Mugavero M, Saag M, et al. 2009. Incomplete peripheral CD4⁺ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. *Clin Infect Dis* **48**: 787–794.
- Kirchhoff F, Greenough TC, Brettler DB, Sullivan JL, Desrosiers RC. 1995. Brief report: Absence of intact nef sequences in a long-term survivor with nonprogressive HIV-1 infection. *N Engl J Med* **332**: 228–232.
- Kirk GD, Merlo C, O'Driscoll P, Mehta SH, Galai N, Vlahov D, Samet J, Engels EA. 2007. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis* **45**: 103–110.
- Kolls JK, Linden A. 2004. Interleukin-17 family members and inflammation. *Immunity* **21**: 467–476.
- Koot M, van Leeuwen R, de Goede RE, Keet IP, Danner S, Eeftink Schattenkerk JK, Reiss P, Tersmette M, Lange JM, Schuitemaker H. 1999. Conversion rate towards a

- syncytium-inducing (SI) phenotype during different stages of human immunodeficiency virus type 1 infection and prognostic value of SI phenotype for survival after AIDS diagnosis. *J Infect Dis* **179**: 254–258.
- Kovacs JA, Lempicki RA, Sidorov IA, Adelsberger JW, Herpin B, Metcalf JA, Sereti I, Polis MA, Davey RT, Tavel J, et al. 2001. Identification of dynamically distinct subpopulations of T lymphocytes that are differentially affected by HIV. *J Exp Med* **194**: 1731–1741.
- Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, Ledergerber B, Lundgren J, Neuhaus J, Nixon D, et al. 2008. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med* **5**: e203. doi: 10.1371/journal.pmed.0050203.
- Lackner AA. 1994. Pathology of simian immunodeficiency virus induced disease. In *Current topics in microbiology and immunology: Simian immunodeficiency virus* (ed. Desrosiers RC, Letvin N), pp. 35–64. Springer-Verlag, Berlin.
- Lackner AA, Vogel P, Ramos RA, Kluge JD, Marthas M. 1994. Early events in tissues during infection with pathogenic (SIVmac239) and nonpathogenic (SIVmac1A11) molecular clones of simian immunodeficiency virus. *Am J Pathol* **145**: 428–439.
- Lane HC, Masur H, Edgar LC, Whalen G, Rook AH, Fauci AS. 1983. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N Engl J Med* **309**: 453–458.
- Lau B, Gange SJ, Moore RD. 2007. Risk of non-AIDS-related mortality may exceed risk of AIDS-related mortality among individuals enrolling into care with CD4⁺ counts greater than 200 cells/mm³. *J Acquir Immune Defic Syndr* **44**: 179–187.
- Lederman MM, Connick E, Landay A, Kuritzkes DR, Spritzler J, St Clair M, Kotzin BL, Fox L, Chiozzi MH, Leonard JM, et al. 1998. Immunologic responses associated with 12 weeks of combination antiretroviral therapy consisting of zidovudine, lamivudine, and zalcitabine: Results of AIDS clinical trials group protocol 315. *J Infect Dis* **178**: 70–79.
- Lederman MM, Rodriguez B, Clagett B, Funderburg N, Medvik K, Gripshover B, Kalayjian RC, Sieg S, Calabrese L. 2010. Immune failure after suppressive ART: High level CD4 and CD8 T cell activation but only memory CD4 cells are cycling. In *18th Conference on Retroviruses and Opportunistic Infections, Abstract 47LB*. Boston.
- Levy JA, Hoffman AD, Kramer SM, Landis JA, Shimabukuro JM, Oshiro LS. 1984. Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS. *Science* **225**: 840–842.
- Li Q, Duan L, Estes JD, Ma ZM, Rourke T, Wang Y, Reilly C, Carlis J, Miller CJ, Haase AT. 2005. Peak SIV replication in resting memory CD4⁺ T cells depletes gut lamina propria CD4⁺ T cells. *Nature* **434**: 1148–1152.
- Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, Fouser LA. 2006. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J Exp Med* **203**: 2271–2279.
- Ling B, Apetrei C, Pandrea I, Veazey RS, Lackner AA, Gormus B, Marx PA. 2004. Classic AIDS in a sooty mangabey after an 18 year natural infection. *J Virol* **78**: 8902–8908.
- Liu R, Paxton WA, Choe S, Ceradini D, Martin SR, Horuk R, MacDonald ME, Stuhlmann H, Koup RA, Landau NR. 1996. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell* **86**: 367–377.
- Liu Z, Cumberland WG, Hultin LE, Prince HE, Detels R, Giorgi JV. 1997. Elevated CD38 antigen expression on CD8⁺ T cells is a stronger marker for the risk of chronic HIV disease progression to AIDS and death in the Multicenter AIDS Cohort Study than CD4⁺ cell count, soluble immune activation markers, or combinations of HLA-DR and CD38 expression. *J Acquir Immune Defic Syndr Hum Retrovirol* **16**: 83–92.
- Liu Z, Cumberland WG, Hultin LE, Kaplan AH, Detels R, Giorgi JV. 1998. CD8⁺ T-lymphocyte activation in HIV-1 disease reflects an aspect of pathogenesis distinct from viral burden and immunodeficiency. *J Acquir Immune Defic Syndr Hum Retrovirol* **18**: 332–340.
- Lum JJ, Cohen OJ, Nie Z, Weaver JG, Gomez TS, Yao XJ, Lynch D, Pilon AA, Hawley N, Kim JE, et al. 2003. Vpr R77Q is associated with long-term nonprogressive HIV infection and impaired induction of apoptosis. *J Clin Invest* **111**: 1547–1554.
- Ma ZM, Abel K, Rourke T, Wang Y, Miller CJ. 2004. A period of transient viremia and occult infection precedes persistent viremia and antiviral immune responses during multiple low-dose intravaginal simian immunodeficiency virus inoculations. *J Virol* **78**: 14048–14052.
- Macal M, Sankaran S, Chun TW, Reay E, Flamm J, Prindiville TJ, Dandekar S. 2008. 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* **1**: 475–488.
- MacDonald TT, Spencer J. 1988. Evidence that activated mucosal T cells play a role in the pathogenesis of enteropathy in human small intestine. *J Exp Med* **167**: 1341–1349.
- MacDonald TT, Spencer J. 1992. Cell-mediated immune injury in the intestine. *Gastroenterol Clin N Am* **21**: 367–386.
- MacDonald TT, Spencer J. 1994. Lymphoid cells and tissues of the gastrointestinal tract. In *Gastrointestinal and hepatic immunology* (ed. Heatley RH), pp. 1–23. Cambridge University Press, Cambridge.
- Manel N, Hogstad B, Wang Y, Levy DE, Unutmaz D, Littman DR. 2010. A cryptic sensor for HIV-1 activates antiviral innate immunity in dendritic cells. *Nature* **467**: 214–217.
- Marchetti G, Bellistri GM, Borghi E, Tincati C, Ferramosca S, La Francesca M, Morace G, Gori A, Monforte AD. 2008. Microbial translocation is associated with sustained failure in CD4⁺ T-cell reconstitution in HIV-infected patients on long-term highly active antiretroviral therapy. *AIDS* **22**: 2035–2038.
- Marin B, Thiebaut R, Bucher HC, Rondeau V, Costagliola D, Dorrucchi M, Hamouda O, Prins M, Walker S, Porter K, et al. 2009. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. *AIDS* **23**: 1743–1753.
- Martin MP, Gao X, Lee JH, Nelson GW, Detels R, Goedert JJ, Buchbinder S, Hoots K, Vlahov D, Trowsdale J, et al.

A.A. Lackner et al.

2002. Epistatic interaction between KIR3DS1 and HLA-B delays the progression to AIDS. *Nat Genet* **31**: 429–434.
- Martinson JA, Montoya CJ, Usuga X, Ronquillo R, Landay AL, Desai SN. 2010. Chloroquine modulates HIV-1-induced plasmacytoid dendritic cell α interferon: Implication for T-cell activation. *Antimicrob Agents Chemother* **54**: 871–881.
- Marx PA, Li Y, Lerche NW, Sutjipto S, Gettie A, Yee JA, Brothman BH, Prince AM, Hanson A, Webster RG, et al. 1991. Isolation of a simian immunodeficiency virus related to human immunodeficiency virus type 2 from a West African pet sooty mangabey. *J Virol* **65**: 4480–4485.
- Masur H, Michelis MA, Greene JB, Onorato I, Stouwe RA, Holzman RS, Wormser G, Brettman L, Lange M, Murray HW, et al. 1981. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: Initial manifestation of cellular immune dysfunction. *N Engl J Med* **305**: 1431–1438.
- Mattapallil JJ, Douek DC, Hill B, Nishimura Y, Martin M, Roederer M. 2005. Massive infection and loss of memory CD4⁺ T cells in multiple tissues during acute SIV infection. *Nature* **434**: 1093–1097.
- McGowan I, Elliott J, Fuerst M, Taing P, Boscardin J, Poles M, Anton P. 2004. Increased HIV-1 mucosal replication is associated with generalized mucosal cytokine activation. *J Acquir Immune Defic Syndr* **37**: 1228–1236.
- Mehandru S, Poles MA, Tenner-Racz K, Horowitz A, Hurley A, Hogan C, Boden D, Racz P, Markowitz M. 2004. Primary HIV-1 infection is associated with preferential depletion of CD4⁺ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med* **200**: 761–770.
- Mehandru S, Poles MA, Tenner-Racz K, Jean-Pierre P, Manuelli V, Lopez P, Shet A, Low A, Mohri H, Boden D, et al. 2006. Lack of mucosal immune reconstitution during prolonged treatment of acute and early HIV-1 infection. *PLoS Med* **3**: e484. doi: 10.1371/journal.pmed.0030484.
- Meier A, Alter G, Frahm N, Sidhu H, Li B, Bagchi A, Teigen N, Streeck H, Stellbrink HJ, Hellman J, et al. 2007. MyD88-dependent immune activation mediated by human immunodeficiency virus type 1-encoded Toll-like receptor ligands. *J Virol* **81**: 8180–8191.
- Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. 1996. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* **272**: 1167–1170.
- Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, Kingsley LA, Todd JA, Saah AJ, Detels R, et al. 1997. Plasma viral load and CD4⁺ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* **126**: 946–954.
- Migueles SA, Laborico AC, Shupert WL, Sabbaghian MS, Rabin R, Hallahan CW, Van Baarle D, Kostense S, Miedema F, McLaughlin M, et al. 2002. HIV-specific CD8⁺ T cell proliferation is coupled to perforin expression and is maintained in nonprogressors. *Nat Immunol* **3**: 1061–1068.
- Migueles SA, Osborne CM, Royce C, Compton AA, Joshi RP, Weeks KA, Rood JE, Berkley AM, Sacha JB, Coglian-Shutta NA, et al. 2008. Lytic granule loading of CD8⁺ T cells is required for HIV-infected cell elimination associated with immune control. *Immunity* **29**: 1009–1021.
- Miller CJ, Li Q, Abel K, Kim EY, Ma ZM, Wietgreffe S, La Franco-Scheuch L, Compton L, Duan L, Shore MD, et al. 2005. Propagation and dissemination of infection after vaginal transmission of simian immunodeficiency virus. *J Virol* **79**: 9217–9227.
- Miura T, Brockman MA, Brumme CJ, Brumme ZL, Carlson JM, Pereyra F, Trocha A, Addo MM, Block BL, Rothchild AC, et al. 2008. Genetic characterization of human immunodeficiency virus type 1 in elite controllers: Lack of gross genetic defects or common amino acid changes. *J Virol* **82**: 8422–8430.
- Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, Gatell J, Rakhmanova A, Johnson M, Kirk O, et al. 2010. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. *J Acquir Immune Defic Syndr* **55**: 262–270.
- Mohri H, Perelson AS, Tung K, Ribeiro RM, Ramratnam B, Markowitz M, Kost R, Hurley A, Weinberger L, Cesar D, et al. 2001. Increased turnover of T lymphocytes in HIV-1 infection and its reduction by antiretroviral therapy. *J Exp Med* **194**: 1277–1287.
- Moore JP, Kitchen SG, Pugach P, Zack JA. 2004. The CCR5 and CXCR4 coreceptors—Central to understanding the transmission and pathogenesis of human immunodeficiency virus type 1 infection. *AIDS Res Hum Retrov* **20**: 111–126.
- Mowat AM, Viney JL. 1997. The anatomical basis of intestinal immunity. *Immunol Rev* **156**: 145–166.
- Murray SM, Down CM, Boulware DR, Stauffer WM, Cavert WP, Schacker TW, Brenchley JM, Douek DC. 2010. Reduction of immune activation with chloroquine therapy during chronic HIV infection. *J Virol* **84**: 12082–12086.
- Neutra MR, Frey A, Kraehenbuhl J-P. 1996. Epithelial M cells: Gateways for mucosal infection and immunization. *Cell* **86**: 345–348.
- Okoye A, Meier-Schellersheim M, Brenchley JM, Hagen SI, Walker JM, Rohankhedkar M, Lum R, Edgar JB, Planer SL, Legasse A, et al. 2007. Progressive CD4⁺ central memory T cell decline results in CD4⁺ effector memory insufficiency and overt disease in chronic SIV infection. *J Exp Med* **204**: 2171–2185.
- Olsson J, Poles M, Spetz AL, Elliott J, Hultin L, Giorgi J, Andersson J, Anton P. 2000. Human immunodeficiency virus type 1 infection is associated with significant mucosal inflammation characterized by increased expression of CCR5, CXCR4, and β -chemokines. *J Infect Dis* **182**: 1625–1635.
- Owen RE, Heitman JW, Hirschhorn DE, Lanteri MC, Biswas HH, Martin JN, Krone MR, Deeks SG, Norris PJ. 2010. HIV⁺ elite controllers have low HIV-specific T-cell activation yet maintain strong, polyfunctional T-cell responses. *AIDS* **24**: 1095–1105.
- Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD. 2006. Mortality in the highly active antiretroviral therapy era: Changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* **43**: 27–34.
- Pandrea I, Sodora DL, Silvestri G, Apetrei C. 2008. Into the wild: Simian immunodeficiency virus (SIV) infection in natural hosts. *Trends Immunol* **29**: 419–428.

- Paranje S, Craigo J, Patterson B, Ding M, Barroso P, Harrison L, Montelaro R, Gupta P. 2002. Subcompartmentalization of HIV-1 quasispecies between seminal cells and seminal plasma indicates their origin in distinct genital tissues. *AIDS Res Hum Retrov* **18**: 1271–1280.
- Picker LJ, Hagen SI, Lum R, Reed-Inderbitzin EF, Daly LM, Sylwester AW, Walker JM, Siess DC, Piatak M Jr, Wang C, et al. 2004. Insufficient production and tissue delivery of CD4⁺ memory T cells in rapidly progressive simian immunodeficiency virus infection. *J Exp Med* **200**: 1299–1314.
- Piconi S, Parisotto S, Capetti A, Passerini S, Argentero B, Terzi R, Meraviglia P, Rizzardini G, Clerici M, Trabattini D. 2011. Hyperimmune bovine colostrum may decrease plasma levels of microbial products and immune activation in untreated HIV infection. In *18th Conference on Retroviruses and Opportunistic Infections, Abstract 382*, Boston.
- Poles MA, Boscardin WJ, Elliott J, Taing P, Fuerst MM, McGowan I, Brown S, Anton PA. 2006. Lack of decay of HIV-1 in gut-associated lymphoid tissue reservoirs in maximally suppressed individuals. *J Acquir Immune Defic Syndr* **43**: 65–68.
- Pope M, Betjes MGH, Romani N, Hirmand H, Cameron PU, Hoffman L, Gezelter S, Schuler G, Steinman RM. 1994. Conjugates of dendritic cells and memory T lymphocytes from skin facilitate productive infection with HIV-1. *Cell* **78**: 389–398.
- Purcell D, Lewin SR, Byakwaga H, French M, Kelleher A, Amin J, Haskleberg H, Kelly M, Cooper D, Emery S. 2011. No correlation between microbial translocation, immune activation, and low-level HIV viremia in HIV-infected individuals with poor CD4⁺ T cell recovery despite suppressive ART. In *18th Conference on Retroviruses and Opportunistic Infections, Abstract 304*. Boston.
- Raffatellu M, Santos RL, Verhoeven DE, George MD, Wilson RP, Winter SE, Godinez I, Sankaran S, Paixao TA, Gordon MA, et al. 2008. Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes *Salmonella* dissemination from the gut. *Nat Med* **14**: 421–428.
- Ramilo O, Bell KD, Uhr JW, Vitetta ES. 1993. Role of CD25⁺ and CD25-T cells in acute HIV infection in vitro. *J Immunol* **150**: 5202–5208.
- Reka S, Garro ML, Kotler DP. 1994. Variation in the expression of human immunodeficiency virus RNA and cytokine mRNA in rectal mucosa during the progression of infection. *Lymphokine Cytok Res* **13**: 391–398.
- Reynolds MR, Rakasz E, Skinner PJ, White C, Abel K, Ma ZM, Compton L, Napoe G, Wilson N, Miller CJ, et al. 2005. CD8⁺ T-lymphocyte response to major immunodominant epitopes after vaginal exposure to simian immunodeficiency virus: Too late and too little. *J Virol* **79**: 9228–9235.
- Rodriguez B, Sethi AK, Cheruvu VK, Mackay W, Bosch RJ, Kitahata M, Boswell SL, Mathews WC, Bangsberg DR, Martin J, et al. 2006. Predictive value of plasma HIV RNA level on rate of CD4 T-cell decline in untreated HIV infection. *JAMA* **296**: 1498–1506.
- Ross MJ, Klotman PE. 2004. HIV-associated nephropathy. *AIDS* **18**: 1089–1099.
- Ryzhova EV, Crino P, Shawyer L, Westmoreland SV, Lackner AA, Gonzalez-Scarano F. 2002. Simian immunodeficiency virus encephalitis: Analysis of envelope sequences from individual brain multinucleated giant cells and tissue samples. *Virology* **297**: 57–67.
- Sachsenberg N, Perelson AS, Yerly S, Schockmel GA, Leduc D, Hirschel B, Perrin L. 1998. Turnover of CD4⁺ and CD8⁺ T lymphocytes in HIV-1 infection as measured by Ki-67 antigen. *J Exp Med* **187**: 1295–1303.
- Salkowitz JR, Purvis SE, Meyerson H, Zimmerman P, O'Brien TR, Aledort L, Eyster ME, Hilgartner M, Kessler C, Konkle BA, et al. 2001. Characterization of high-risk HIV-1 seronegative hemophiliacs. *Clin Immunol* **98**: 200–211.
- Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, Saragosti S, Lapoumeroulie C, Cogniaux J, Forceille C, et al. 1996. Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* **382**: 722–725.
- Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, Pedersen C, Ruxrungtham K, Lewin SR, Emery S, et al. 2011. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis* **203**: 780–790.
- Sankaran S, Guadalupe M, Reay E, George MD, Flamm J, Prindiville T, Dandekar S. 2005. Gut mucosal T cell responses and gene expression correlate with protection against disease in long-term HIV-1-infected nonprogressors. *Proc Natl Acad Sci* **102**: 9860–9865.
- Sankaran S, George MD, Reay E, Guadalupe M, Flamm J, Prindiville T, Dandekar S. 2008. Rapid onset of intestinal epithelial barrier dysfunction in primary human immunodeficiency virus infection is driven by an imbalance between immune response and mucosal repair and regeneration. *J Virol* **82**: 538–545.
- Sasseville VG, Du Z, Chalifoux IV, Pauley DR, Young HL, Sehgal PK, Desrosiers RC, Lackner AA. 1996. Induction of lymphocyte proliferation and severe gastrointestinal disease in macaques by a *nef* gene variant of SIVmac239. *Am J Pathol* **149**: 163–176.
- Schacker T, Collier AC, Hughes J, Shea T, Corey L. 1996. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med* **125**: 257–264.
- Schacker TW, Nguyen PL, Beilman GJ, Wolinsky S, Larson M, Reilly C, Haase AT. 2002. Collagen deposition in HIV-1 infected lymphatic tissues and T cell homeostasis. *J Clin Invest* **110**: 1133–1139.
- Schacker TW, Reilly C, Beilman GJ, Taylor J, Skarda D, Krause D, Larson M, Haase AT. 2005. Amount of lymphatic tissue fibrosis in HIV infection predicts magnitude of HAART-associated change in peripheral CD4 cell count. *AIDS* **19**: 2169–2171.
- Schieferdecker HL, Ullrich R, Hirsland H, Zeitz M. 1992. T cell differentiation antigens on lymphocytes in the human intestinal lamina propria. *J Immunol* **149**: 2816–2822.
- Shanahan F. 1999. Intestinal lymphoepithelial communication. *Adv Exp Med Biol* **473**: 1–9.
- Shannon RP. 2001. SIV cardiomyopathy in non-human primates. *Trends Cardiovasc Med* **11**: 242–246.
- Sheth PM, Chege D, Shin IY, Huibner S, Yue FY, Loutfy M, Halpenny R, Persad D, Kovacs C, Chun TW, et al. 2008.

A.A. Lackner et al.

- Immune reconstitution in the sigmoid colon after long-term HIV therapy. *Mucosal Immunol* **1**: 382–388.
- Shive C, Lederman MM, Calabrese L, Funderburg N, Bonilla H, Gripshover B, Salata RA, McComsey GA, Claggett B, Medvik K, et al. 2011. Immunologic failure despite suppressive antiretroviral therapy (ART) is related to increased inflammation and evidence of microbial translocation. In *18th Conference on Retroviruses and Opportunistic Infections, Abstract 320*. Boston.
- Sieg SF, Rodriguez B, Asaad R, Jiang W, Bazdar DA, Lederman MM. 2005. Peripheral S-phase T cells in HIV disease have a central memory phenotype and rarely have evidence of recent T cell receptor engagement. *J Infect Dis* **192**: 62–70.
- Sieg SF, Bazdar DA, Lederman MM. 2008. S-phase entry leads to cell death in circulating T cells from HIV-infected persons. *J Leukocyte Biol* **83**: 1382–1387.
- Siegal FP, Lopez C, Hammer GS, Brown AE, Kornfeld SJ, Gold J, Hassett J, Hirschman SZ, Cunningham-Rundles C, Adelsberg BR, et al. 1981. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med* **305**: 1439–1444.
- Silvestri G, Sodora DL, Koup RA, Paiardini M, O'Neil SP, McClure HM, Staprans SI, Feinberg MB. 2003. Non-pathogenic SIV infection of sooty mangabeys is characterized by limited bystander immunopathology despite chronic high-level viremia. *Immunity* **18**: 441–452.
- Spira AI, Marx PA, Patterson BK, Mahoney J, Koup RA, Wolinsky SM, Ho DD. 1996. Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. *J Exp Med* **183**: 215–225.
- Steinman L. 2007. A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. *Nat Med* **13**: 139–145.
- Stevceva L, Kelsall B, Nacs J, Moniuszko M, Hel Z, Tryniszewska E, Franchini G. 2002. Cervicovaginal lamina propria lymphocytes: Phenotypic characterization and their importance in cytotoxic T-lymphocyte responses to simian immunodeficiency virus SIVmac251. *J Virol* **76**: 9–18.
- Stevenson M, Stanwick TL, Dempsey MP, Lamonica CA. 1990. HIV-1 replication is controlled at the level of T cell activation and proviral integration. *EMBO J* **9**: 1551–1560.
- Stone JD, Heise CC, Miller CJ, Halsted CH, Dandekar S. 1994. Development of malabsorption and nutritional complications in simian immunodeficiency virus-infected rhesus macaques. *AIDS* **8**: 1245–1256.
- Tang J, Costello C, Keet IP, Rivers C, Leblanc S, Karita E, Allen S, Kaslow RA. 1999. HLA class I homozygosity accelerates disease progression in human immunodeficiency virus type 1 infection. *AIDS Res Hum Retrov* **15**: 317–324.
- Tilling R, Kinloch S, Goh LE, Cooper D, Perrin L, Lampe F, Zaunders J, Hoen B, Tsoukas C, Andersson J, et al. 2002. Parallel decline of CD8⁺/CD38⁺⁺ T cells and viraemia in response to quadruple highly active antiretroviral therapy in primary HIV infection. *AIDS* **16**: 589–596.
- Traber PG. 1997. Epithelial cell growth and differentiation. V. Transcriptional regulation, development, and neoplasia of the intestinal epithelium. *Am J Physiol* **273**: G979–G981.
- Trautmann L, Janbazian L, Chomont N, Said EA, Gimmig S, Bessette B, Boulassel MR, Delwart E, Sepulveda H, Balderas RS, et al. 2006. Upregulation of PD-1 expression on HIV-specific CD8⁺ T cells leads to reversible immune dysfunction. *Nat Med* **12**: 1198–1202.
- Triant VA, Lee H, Hadigan C, Grinspoon SK. 2007. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* **92**: 2506–2512.
- Turner JR. 2006. Molecular basis of epithelial barrier regulation: From basic mechanisms to clinical application. *Am J Pathol* **169**: 1901–1909.
- Turner JR. 2009. Intestinal mucosal barrier function in health and disease. *Nat Rev Immunol* **9**: 799–809.
- Ullrich R, Zeitz M, Heise W, L'age M, Hoffken G, Riecken EO. 1989. Small intestinal structure and function in patients infected with human immunodeficiency virus (HIV): Evidence for HIV-induced enteropathy. *Ann Intern Med* **111**: 15–21.
- van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F. 2010. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS* **24**: 1527–1535.
- Veazey RS. 2003. Vaginal CD4⁺ T cells express high levels of CCR5 and are rapidly depleted in simian immunodeficiency virus infection. *J Infect Dis* **187**: 769–776.
- Veazey RS, Rosenzweig M, Shvetz DE, Pauley DR, DeMaria M, Chalifoux IV, Johnson RP, Lackner AA. 1997. Characterization of gut-associated lymphoid tissue (GALT) of normal rhesus macaques. *Clin Immunol Immunopathol* **82**: 230–242.
- Veazey RS, DeMaria M, Chalifoux IV, Shvetz DE, Pauley DR, Knight HL, Rosenzweig M, Johnson RP, Desrosiers RC, Lackner AA. 1998. Gastrointestinal tract as a major site of CD4⁺ T cell depletion and viral replication in SIV infection. *Science* **280**: 427–431.
- Veazey RS, Mansfield KG, Tham IC, Carville AC, Shvetz DE, Forand AE, Lackner AA. 2000a. Dynamics of CCR5 expression by CD4⁺ T cells in lymphoid tissues during SIV infection. *J Virol* **74**: 11001–11007.
- Veazey RS, Tham IC, Mansfield KG, DeMaria M, Forand AE, Shvetz DE, Chalifoux IV, Sehgal PK, Lackner AA. 2000b. Identifying the target cell in primary SIV infection: Highly activated “memory” CD4⁺ T cells are rapidly eliminated in early SIV infection in vivo. *J Virol* **74**: 57–64.
- Veazey RS, Gaudin M-C, Mansfield KG, Tham IC, Altman JD, Lifson JD, Lackner AA, Johnson RP. 2001a. Emergence of simian immunodeficiency virus-specific CD8⁺ T cells in the intestine of macaques during primary infection. *J Virol* **75**: 10515–10519.
- Veazey RS, Marx PA, Lackner AA. 2001b. The mucosal immune system: Primary target for HIV infection and fundamental component of AIDS pathogenesis. *Trends Immunol* **22**: 626–633.
- Veazey RS, Marx PA, Lackner AA. 2002. Importance of the state of activation and/or differentiation of CD4⁺ T cells in AIDS pathogenesis. *Trends Immunol* **23**: 129.

- Veazey RS, Lifson JD, Schmitz JE, Kuroda MJ, Piatak M, Pandrea I, Purcell J, Bohm R, Blanchard J, Williams KC, et al. 2003. Dynamics of simian immunodeficiency virus-specific cytotoxic T-cell responses in tissues. *J Med Primatol* **32**: 194–200.
- Viney J, MacDonald TT, Spencer J. 1990. γ/δ T cells in the gut epithelium. *Gut* **31**: 841–844.
- Weber CR, Turner JR. 2007. Inflammatory bowel disease: Is it really just another break in the wall? *Gut* **56**: 6–8.
- Weber R, Friis-Moller N, Sabin C, Reiss P, Monforte A, Dabis F, El-Sadr WM, De Wit S, Morfeldt L, Law M, et al. 2005. HIV and non-HIV-related deaths and their relationship to immunodeficiency: The D:A:D study. In *12th Conference on Retroviruses and Opportunistic Infections, Abstract 595*. Boston.
- Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, Dabis F, Law MG, Pradier C, De Wit S, et al. 2006. Liver-related deaths in persons infected with the human immunodeficiency virus: The D:A:D study. *Arch Intern Med* **166**: 1632–1641.
- Westmoreland SV, Halpern E, Lackner AA. 1998. Simian immunodeficiency virus encephalitis in rhesus macaques is associated with rapid disease progression. *J Neurovirol* **4**: 260–268.
- Wilson CM, Ellenberg JH, Douglas SD, Moscicki AB, Holland CA. 2004. CD8⁺CD38⁺ T cells but not HIV type 1 RNA viral load predict CD4⁺ T cell loss in a predominantly minority female HIV⁺ adolescent population. *AIDS Res Hum Retrov* **20**: 263–269.
- Woelk CH, Ottone F, Plotkin CR, Du P, Royer CD, Rought SE, Lozach J, Sasik R, Kornbluth RS, Richman DD, et al. 2004. Interferon gene expression following HIV type 1 infection of monocyte-derived macrophages. *AIDS Res Hum Retrov* **20**: 1210–1222.
- Wykrzykowska JJ, Rosenzweig M, Veazey RS, Simon MA, Halvorsen K, Desrosiers RC, Johnson RP, Lackner AA. 1998. Early regeneration of thymic progenitors in rhesus macaques infected with simian immunodeficiency virus. *J Exp Med* **187**: 1767–1778.
- Yadavalli GK, Lederman MM, Sieg S, Funderburg N, Clagett B, Medvik K, Salata RA, Gripshover B, Fulton S, Rodriguez B. 2011. Hyperimmune bovine colostrum may decrease plasma levels of microbial products and immune activation in untreated HIV infection. In *6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Abstract 3842*. Rome.
- Yan N, Regalado-Magdos AD, Stiggelbout B, Lee-Kirsch MA, Lieberman J. 2010. The cytosolic exonuclease TREX1 inhibits the innate immune response to human immunodeficiency virus type 1. *Nat Immunol* **11**: 1005–1013.
- Zack JA, Arrigo SJ, Weitsman SR, Go AS, Haislip A, Chen IS. 1990. HIV-1 entry into quiescent primary lymphocytes: Molecular analysis reveals a labile, latent viral structure. *Cell* **61**: 213–222.
- Zagury D, Bernard J, Leonard R, Cheynier R, Feldman M, Sarin PS, Gallo RC. 1986. Long-term cultures of HTLV-III-infected T cells: A model of cytopathology of T-cell depletion in AIDS. *Science* **231**: 850–853.
- Zeitl M, Greene WC, Peffer NJ, James SP. 1988. Lymphocytes isolated from the intestinal lamina propria of normal nonhuman primates have increased expression of genes associated with T-cell activation. *Gastroenterol* **94**: 647–655.

HIV Pathogenesis: The Host

A.A. Lackner, Michael M. Lederman and Benigno Rodriguez

Cold Spring Harb Perspect Med 2012; doi: 10.1101/cshperspect.a007005 originally published online April 17, 2012

Subject Collection [HIV](#)

HIV Pathogenesis: Dynamics and Genetics of Viral Populations and Infected Cells

John Coffin and Ronald Swanstrom

Human Immunodeficiency Virus Vaccine Trials

Robert J. O'Connell, Jerome H. Kim, Lawrence Corey, et al.

HIV Transmission

George M. Shaw and Eric Hunter

Novel Cell and Gene Therapies for HIV

James A. Hoxie and Carl H. June

Behavioral and Biomedical Combination Strategies for HIV Prevention

Linda-Gail Bekker, Chris Beyrer and Thomas C. Quinn

HIV-1 Assembly, Budding, and Maturation

Wesley I. Sundquist and Hans-Georg Kräusslich

HIV-1 Assembly, Budding, and Maturation

Wesley I. Sundquist and Hans-Georg Kräusslich

Lessons in Nonhuman Primate Models for AIDS Vaccine Research: From Minefields to Milestones

Jeffrey D. Lifson and Nancy L. Haigwood

HIV-1 Pathogenesis: The Virus

Ronald Swanstrom and John Coffin

The T-Cell Response to HIV

Bruce Walker and Andrew McMichael

HIV-1 Reverse Transcription

Wei-Shau Hu and Stephen H. Hughes

HIV Pathogenesis: The Host

A.A. Lackner, Michael M. Lederman and Benigno Rodriguez

HIV: Cell Binding and Entry

Craig B. Wilen, John C. Tilton and Robert W. Doms

Innate Immune Control of HIV

Mary Carrington and Galit Alter

HIV DNA Integration

Robert Craigie and Frederic D. Bushman

HIV-1-Related Central Nervous System Disease: Current Issues in Pathogenesis, Diagnosis, and Treatment

Serena Spudich and Francisco González-Scarano

For additional articles in this collection, see <http://perspectivesinmedicine.cshlp.org/cgi/collection/>