HIV Pathogenesis: The Host

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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 homozgyosity 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. 1990) 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...
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/μL 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
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 γδ 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
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.
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 three-fold) 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 (Vezey 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 (Vezey 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 (Vezey 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 coinfected 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 (Vezey 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
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. Hypergrobulinemia and increased circulating levels of proinflammatory cytokines are characteristic, and although type I 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). 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 (Pickel 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...
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 of microbial products from damaged gut 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).

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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-
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](http://perspectivesinmedicine.cshlp.org/)

**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.

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