Immunodeficiency lentiviral infections in natural and non-natural hosts

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The host immune system is profoundly affected during the acute phase of progressive immunodeficiency lentiviral infections. Studies of these alterations have been quite restricted in humans because of the limited availability of samples from acutely HIV-infected persons. Therefore, numerous studies have turned attention to nonhuman primate models. Specifically, SIV-infected rhesus macaques (RM) have been informative for understanding the pathogenesis of HIV infection in humans. Indeed, advantages of the nonhuman primate model include the ability to study the very early events after infection and the ability to retrieve copious amounts of tissues. In addition, nonhuman primates allow for comparative studies between non-natural and natural hosts for SIV, in which SIV infection results in progression, or not, to AIDS, respectively. Although SIV infection of RM is the best model for HIV infection, the immunologic and/or virologic phenomena in SIV-infected RM do not always reflect those seen in HIV-infected humans. Here virologic and immunologic aspects of acute HIV infection of humans and SIV infection of Asian and African nonhuman primates are discussed and compared in relation to how these aspects relate to disease progression. (Blood. 2011;118(4):847-854)

Patterns of viral replication

Progressive HIV infection in humans and simian immunodeficiency virus (SIV) infection in Asian macaques arise from cross-species transmission of viruses known to naturally infect nonhuman primates in Africa (referred to as natural hosts for SIV).1 These primate immunodeficiency lentiviruses replicate very efficiently in vivo.2 In the majority of infected persons, the virus replicates to levels that approach 10 million virions per milliliter of plasma during the acute phase of infection.3 These high levels of viral replication are similar among acutely HIV-infected humans, SIV-infected Asian macaques, and SIV-infected natural hosts, such as sooty mangabeys (SM) and African green monkeys (AGM; Figure 1A). As the infection course advances into the chronic phase of infection, the levels of viremia in plasma decrease, in general, by at least 2 logs in humans, Asian macaques, and African nonhuman primates. However, although the levels of acute plasma viremia are similar in all hosts, there is some disconnect during the chronic phase of infection, with HIV-infected persons and SIV-infected natural hosts showing levels of plasma viremia generally lower than those observed in SIV-infected Asian macaques (Figure 1A).3 Regardless, it is clear that viral replication is rampant during the acute phase of infection and moderately wanes as the infection advances into the chronic phase in both progressive and nonprogressive infections and that the nonprogressing phenotype of natural SIV infections cannot simply be attributed to lower levels of virus replication. Hence, high levels of virus replication are not sufficient to cause progression to AIDS.

In addition to the levels of viral replication, another important parameter to consider is the cytotoxicity of the viruses. In several studies, the cytotoxic potential of HIV or SIV in different hosts has been determined using mathematical modeling of infected cell life span, in vivo, by analysis of viremia before and after initiation of antiretroviral therapy. When these studies were performed in chronic HIV-infected persons, the bulk of HIV replication (92%-99%) was found to occur in short-lived cells, with a determined half-life of productively infected CD4 T-cell of 0.7 to 1 day.4,5 Very similar data were obtained in SIV-infected macaques, in which the estimate half-life of productively infected cells ranged between 0.37 and 0.50 day in a study using quadruple antiretroviral therapy.6 Recently, the same experimental approach was used to assess the turnover of virus and infected cells in natural hosts for SIV. Remarkably, in SIV-infected SM and AGM, the bulk (92%-99%) of virus replication occurs in short-lived cells, with the average in vivo half-life of infected cells being 1.06 days and 4 to 9.5 hours, respectively.7 Collectively, these data suggest that SIVsmm and SIVagm are cytopathic in vivo in natural SIV infections and that the preservation of CD4 T-cell homeostasis and AIDS resistance of SIV-infected natural hosts is unlikely to be simply because of a longer life span of infected cells.

Anatomically restricted CD4 T-cell depletion

CD4 T-cell depletion is a hallmark of progressive immunodeficiency lentiviral infections. Peripheral blood CD4 T-cell numbers falling below 200 cells/μL of blood is coincident with the onset of opportunistic infections. Loss of CD4 T cells from peripheral blood during the chronic phase of infection is generally quite slow with HIV-infected humans and SIV-infected RM, losing approximately 40 CD4 T cells per microliter of blood per year.8,9 However, there is significantly more severe depletion of CD4 T cells within the gastrointestinal (GI) tract.10-13 Indeed, the majority of CD4 T cells within the GI tract, particularly those expressing the HIV coreceptor CCR5, are depleted during the acute phase of infection (Figure 1B). Because of the large surface area of the GI tract, this massive depletion of CD4 T cells during the acute phase of infection reflects loss of most of the CD4 T cells within the body. The understanding of the...
overall impact of mucosal immune dysfunction in HIV pathogenesis is complicated by the impracticability to perform longitudinal investigation and/or to sample multiple anatomic sites in HIV-infected persons. Indeed, in the majority of studies on humans, only one or 2 GI anatomic sites were sampled, thus compromising the ability to obtain a truly informative analysis of the intestinal immune system. To overcome these limitations, numerous studies have turned attention to nonhuman primates. These studies have shown that the massive acute phase depletion of GI tract CD4 T cells is common among acutely SIV-infected RM and HIV-infected humans (Figure 1B). Of note, a recent study comparing multiple GI anatomic sites showed significant anatomic-specific differences in the extent of CD4 T-cell depletion in SIV-infected RM. Indeed, even across the GI tract, CD4 T-cell depletion in chronically SIV-infected RM was more severe in the small intestine relative to the large intestine. Similar comparative analysis has not systematically been performed using human samples, and it is therefore unclear whether this phenomenon is restricted to SIV-infected RM.

Similar to progressive HIV/SIV infections in humans and macaques, nonprogressive SIV infections of African nonhuman primates are characterized by an acute loss of mucosal CD4 T cells (Figure 1B). Indeed, nonprogressive SIV infections of natural hosts are characterized by long-term maintenance of circulating CD4 T cells and lack of disease progression. Although mucosal CD4 T-cell depletion is a common feature of pathogenic and nonpathogenic lentiviral infections, it is to note that the extent of this depletion is less dramatic in AGM and SM than in progressive HIV/SIV infections. Indeed, whereas depletion of mucosal CD4 T cells increases with disease progression in HIV-infected humans and SIV-infected RM, in natural hosts the levels of mucosal CD4 T cells remain stable (in SM) or even increase (in AGM) in the chronic phase of infection (Figure 1B).12,13 Intriguingly, SIV-induced CD4 T-cell depletion, itself, does not render SM susceptible to opportunistic infections as recent studies have identified CCR5/CXCR4-tropic strains of SIVsmm, which cause massive mucosal and peripheral CD4 T-cell depletion in infected SM. The immunologic mechanisms underlying the lack of disease progression in CD4-depleted SM remain unclear, but these animals may maintain effector functions normally attributed to CD4 T cells, similar to what is observed in AGMs who have very low numbers of CD4 T cells.

Phenotypically restricted CD4 T-cell depletion

HIV and SIV are clearly tropic for very specific subsets of lymphocytes. Indeed, CD4 T cells are preferred targets for HIV and SIV in vivo in both progressive and nonprogressive infections. Moreover, CCR5 is the dominant coreceptor used by most HIV and SIV strains renders CD4 T cells that express CCR5 more likely to be infected and depleted during the course of progressive HIV and SIV infections. Because CCR5 is not expressed by naive CD4 T cells, these cells are relatively spared from infection and depletion. Most transmitted viruses are CCR5 tropic, and studies of acutely SIV-infected RM have shown that the majority of all CCR5 memory CD4 T cells, which reside within the GI tract, are infected and subsequently depleted in < 3 weeks of infection. Moreover, studies of HIV-infected humans have also demonstrated massive gastrointestinal CD4 T-cell depletion during the acute phase of infection.

In addition to CCR5, the expression of the α4β7 integrin heterodimer has been suggested as an important cofactor for the efficacy of HIV and SIV to infect and replicate on CD4 T cells. α4β7 and CCR9 are among cell surface “homing” molecules that have received attention because of their importance in promoting trafficking of the cells to the GI tract. A putative role for α4β7 in AIDS pathogenesis is highlighted by the fact that (1) gut mucosa is the primary site for HIV infection and T-cell destruction and (2) it apparently binds to HIV with consequent signaling cascades.

Recent studies on RM showed that, although virtually all gut CD4 T cells express α4β7, but at different levels, approximately 25% of CD4 T cells are β7hi and the remaining 75% show a β7int phenotype. Furthermore, these studies showed that peripheral and gut mucosa CD4 T cells expressing high levels of α4β7 are preferentially depleted and are more frequently infected by the virus in vivo than their β7int (blood) or β7low (gut) counterparts. These β7hi cells serve as the main SIV targets during the acute phase of infection. The recent findings that human α4β7 CD4 T cells that express high levels of CCR5 and Ki-67 are more susceptible to productive infection than CD4 T cells that are α4β7low are consistent with this view.

Of note, in a recent study, Ansari et al treated RM with a recombinant RM monoclonal antibody against α4β7 before and during acute SIV infection. Remarkably, anti-α4β7-treated SIV-infected RM showed a significant decrease in plasma and GI

Figure 1. Variations in the main virologic and immunologic markers of HIV/SIV infection during the course of pathogenic HIV/SIV infections in humans (black lines) and SM (blue lines), and nonprogressive SIV infection in SM (red lines) and AGM (green lines). (A) Levels of viral replication (solid lines) and immune activation (dotted lines), defined as levels of T- and B-cell activation/proliferation, Interferon stimulates gene response, type I interferon production. (B) Levels of CD4 T cells in peripheral blood (solid lines) and gastrointestinal tracts (mucosa-associated lymphoid tissue [MALT], dotted lines). (C) Levels of mucosal Th17 cells (solid lines, defined as IL-17–producing CD4 T cells) and integrity of the epithelial barrier at the mucosal level (dotted lines). Data on epithelial barrier integrity during the acute phase of infection are available only for SM.
maintain IL-17–producing CD4 T cells within the GI tracts of infected animals. Another subset of CD4 T cells, those producing IL-21, has very recently received attention because of the important role of this cytokine in regulating Th17 cell homeostasis, increasing CD8 T-cell numbers and functionality, and helping control chronic viral infections.8,39 Two recent studies that investigated IL-21–producing T cells in HIV infection provided different conclusions, with the levels of circulating IL-21–producing CD4 T cells in HIV-infected persons being decreased compared with uninfected controls in one study,40 but increased in the other.41

Although it seems probable that the insult to the mucosal immune system results in microbial translocation, the relative contribution of microbial translocation and other factors to immune activation is not completely understood. The effectiveness of therapeutic interventions that decrease microbial translocation–induced immune activation is a tempting, although as yet, unknown avenue to pursue. Indeed, a recent study in chronically HIV-infected humans showed that supplementation of highly active antiretroviral therapy with probiotic bacteria led to improved reconstitution of peripheral blood CD4 T cells.42

### Functional abnormalities of T cells

In addition to the phenotype-specific depletion of CD4 T cells that occurs during progressive HIV and SIV infections, several studies have recently demonstrated functional abnormalities among T cells from infected persons. Specifically, the ability of Th1 type T cells to simultaneously produce multiple effector cytokines, such as IL-2, TNF-α, and IFN-γ, is decreased among CD4 T cells from progressively HIV/SIV-infected subjects compared with uninfected subjects.28,30 These functional abnormalities are not solely attributed to direct viral infection as functional abnormalities are also observed among CD8 T cells (which are only rarely infected by the virus in vivo).20,28 Hence, loss of functionality among both CD4 and CD8 memory T cells may, in part, underlie the immunodeficiency associated with progressive HIV/SIV infections.

In addition to an overall decrease in functionality of Th1 type CD4 and CD8 T cells in the peripheral blood of progressively HIV- and SIV-infected persons, recent data have also shown alterations in T-cell functionality within the GI tract. Th17 CD4 T cells, producing IL-17 and IL-22 in response to stimulation through the T-cell receptor, have been recently identified.31 IL-17 and IL-22 function in vivo to promote recruitment of neutrophils to areas of bacterial infection, to induce proliferation of enterocytes and production of antibacterial defenses.32,33 Therefore, Th17 cells are thought to play an important role in antibacterial immunity, and these cells are relatively concentrated at mucosal sites compared with peripheral blood.35 Remarkably, Th17 cells are present at significantly lower frequencies in the GI tracts of chronically HIV/SIV-infected persons compared with uninfected persons.35,36 Hence, the specific loss of this functionally defined subset of CD4 T cells may render chronically HIV/SIV-infected persons less capable of controlling against translocated microbial products and less capable of maintaining an integral tight epithelial barrier (Figure 1C). However, the rapidity of this preferential Th17 cell loss, relative to infection, and the mechanisms underlying this preferential loss remain unclear. The importance of preferential Th17 cell loss from the GI tracts for disease progression is highlighted by the relative preservation of GI tract Th17 cells in chronically SIV-infected SM and AGM (Figure 1C).37 Hence, coevolution of natural hosts with SIV has involved a mechanism to

### Adaptive immune activation

One of the hallmarks of progressive HIV and SIV infections is a pathologic activation of the immune system. Indeed, the degree of T-cell activation predicts disease progression better than either plasma viral load or peripheral blood CD4 T-cell count.43 Throughout the course of progressive infection T cells, both CD4 and CD8 are abnormally activated, as manifested by (1) increased turnover, as determined by Ki-67 expression and decay of cells labeled in vivo;44, (2) increased frequencies of T cells with an activated (CD38+HLADR+) or “exhausted” and senescent phenotype (based on expression of CD57, PD-1, Tim-3, and/or LAG-3)45,46; and (3) increased frequencies of apoptotic T cells.49 Other markers of immune activation associated with HIV infection are represented by increased production of proinflammatory and proapoptotic cytokines, morphologic changes in the lymph node and/or bone marrow architecture.50 The deleterious nature of immune activation during the chronic phase of progressive infection is unclear but probably involves production of activated CD4 T-cell targets for the virus, attrition of the memory CD4 T-cell pool, and accumulation of high frequencies of terminally differentiated and exhausted memory T and B cells.51,52

Activation of the immune system is clearly not limited to the T-cell pool. Indeed, activation of B cells is also observed in chronically infected persons.53–55 This abnormal B-cell activation is associated with compromised B-cell responses to vaccination.56 Hence, immune activation may, over time, result in an impaired ability to respond immunologically to pathogens. This phenomenon may, in part, explain the tight associations between immune activation and disease progression.

During HIV/SIV infection, the degree of immune activation roughly follows that of plasma viremia with the highest levels of both being observed during the acute phase of infection (Figure 1A).57 Of note, increased T-cell turnover is observed during the acute phase of both progressive and nonprogressive infections. However, consistent with persistent immune activation being closely associated with disease progression in HIV/SIV-infected humans and RM, SIV-infected natural hosts, such as SM and AGM, lack any obvious signs of elevated immune activation during the chronic phase of infection (Figure 1A).58,59
Table 1. The role of adaptive immune response in restricting virus replication and affecting disease progression has been investigated by in vivo studies of CD8, B, or CD8 and B-cell depletion

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<th>Viral load</th>
<th>AIDS progression</th>
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<td>Natural hosts (AGM/SM)</td>
<td>Non-natural hosts (RM/PTM)</td>
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<td>CD8 cell depletion</td>
<td>Brief increase</td>
<td>~ 1.5 log increase</td>
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<td>B-cell depletion</td>
<td>No effect</td>
<td>Unclear: Increase^76</td>
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<td>CD8 and B-cell depletion</td>
<td>Brief increase</td>
<td>1 log increase peak; 4 log increase set-point</td>
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Comparison of the effects induced by these depletions in natural and non-natural hosts for SIV. AGM/SM indicates African green monkey/sooty mangabey; and RM/PTM, rhesus macaque/pigtail macaque.

In summary, the lack of chronic immune activation is a key feature distinguishing natural from non-natural hosts for lentiviral infections. Unfortunately, how SIV-infected SM and AGM avoid aberrant chronic immune activation, despite having acute immune activation and levels of virus replication comparable with those described in humans and RM, remains unclear.

**Innate immune activation**

Based on in vitro stimulation of dendritic cells with particular Toll-like receptor antagonists, recent data have suggested that one of the mechanisms underlying nonprogressive SIV infection of natural hosts is their innate inability to respond to such stimulations with production of type I interferon.60 Hence, nonresponsiveness of the immune system during the acute phase of infection may set the stage for a nonprogressive disease. However, analysis of type I INF-related genes has shown that such immune activation is practically indistinguishable between progressive SIV infection of Asian macaques and nonprogressive SIV infections of AGM and SM.61

**Antivirus specific immune responses**

Although polyfunctional T-cell responses have been associated with control of viral replication in humans and RM, such polyfunctional T-cell responses are not required to prevent a progressive disease course. Indeed, in SIVagm-infected AGM and SIVsmm-infected SM, polyfunctional T-cell responses against the virus are not superior compared with progressively infected humans and Asian macaques.62,63 However, it is clear that CD8 T cells specific for the virus are capable of exerting immunologic pressure against the virus. Indeed, mapping individual, epitope-specific, CD8 T-cell responses against HIV and different SIVs have revealed linear epitopes of the viruses that are recognized by antigen-specific CD8 T cells. By sequence analysis of plasma viral RNA, it is clear that these epitopes become mutated in both SIV-infected natural hosts and HIV/SIV-infected humans and RM.64,65 Moreover, it is clear that these CD8 T-cell responses against the virus are initiated during the acute phase of infection, given the early emergence of mutations of amino acids recognized by these CD8 T cells.66

Although CD8 T cells against the virus are elicited in both pathogenic and nonpathogenic infections, their relative role in protecting against disease progression appears to differ between the two. Indeed, the rare HIV-infected persons who manifest a nonprogressive disease course tend to have very low (often undetectable) levels of virus in plasma.67 Many of these persons express HLA-B5701, and numerous studies have suggested that viral replication is controlled to undetectable levels via CD8 T-cell responses68,69; however, other genetic factors have been associated with a nonprogressive phenotype (discussed in more detail in “Genetic determinants”). Although nonprogressive infection of humans tends to be associated with an apparent CD8 T cell-mediated response against the virus, such cell-mediated control does not seem to occur in nonprogressively infected natural hosts for SIV. Hence, although SIV-infected natural hosts immunologically respond to the virus with T-cell responses,63 these do not appear to play a significant role in controlling viral replication. Indeed, there are only very moderate effects (specifically within the acute phase of infection) on viral replication after experimental depletion of CD8 lymphocytes in SIV-infected natural hosts (Table 1).69,70

It is clear that, during progressive HIV infection of humans, production of HIV-specific antibodies is insufficient in controlling viral replication. During the acute phase of infection, the B-cell response is mainly directed to non-neutralizing epitopes of the HIV envelope, and during the chronic phase of infection the virus rapidly escapes would be neutralizing antibodies.71 The molecular, cellular, and pathophysiolgy mechanisms underlying the ineffective antibody response to HIV are complex, multifactorial, and still poorly understood. There is, however, a wide consensus that an important role is played by the numerous defects of B cells that arise in HIV-infected persons, such as functional exhaustion, polyclonal activation, loss of memory B cells, and paucity of virus-specific IgA at mucosal sites, where HIV transmission and acute viral replication occur.53,55,72 Other factors critically contributing to the ineffective antibody response are the high degree of HIV diversity, the poor immunologic access to conserved HIV env regions, and the rapid viral mutation rate.71

Studies in SIV-infected SM and AGM suggest that AIDS resistance in these primates is not the result of a more effective humoral immune response, with the levels of anti-SIV binding and neutralizing antibodies being similar, or even slightly lower, than those described in HIV-infected humans.73,74 Indeed, when the ability to mount neutralizing antibodies against autologous virus was compared in SIV-infected SM and HIV (subtype C)–infected humans, SM showed lower titers of autologous antibodies.75 Furthermore, and in contrast to that found in RM,75 passive immunoglobulin transfer does not protect AGM against SIVagm infection.71 To elucidate better the role of humoral immune responses in restricting virus replication and to investigate whether these responses play a role in the lack of disease progression in natural hosts, several in vivo studies of prolonged B-cell depletion in natural (AGM) and non-natural (RM and pigtail macaques [PTM]) hosts for SIV have been performed. Although conflicting results were obtained in SIV-infected RM, with some studies indicating a role of B cells in controlling post peak viral load and
disease progression\textsuperscript{65,77} and others showing a more limited impact,\textsuperscript{78} it is clear that antibody-mediated control during natural infection is not efficient. Indeed, the data were more consistent for AGM, in which successful depletion of B cells in blood, lymph, node, and intestine, with effective suppression of antibody production, did not impact the levels of viral replication and the course of disease progression (Table 1).\textsuperscript{69,79} Recent studies have depleted adaptive immune responses in acute infection in PTM and AGM by depletion of both CD8\textsuperscript{+} and CD20\textsuperscript{+} lymphocytes. Whereas PTM showed higher viremia (1-log increase in peak viremia and 4-log increase in set-point viremia) and faster progression to AIDS, AGM experienced only a short prolongation of peak viremia, but these animals had similar set-point viremia and no opportunistic infections or signs of illness (Table 1).\textsuperscript{69}

Collectively, these studies indicate that, although adaptive immune responses are critical for viral containment and for controlling disease progression in pathogenic lentiviral infections, they do not play a key role in protecting SIV-infected natural hosts from disease progression.

**Genetic determinants**

The clinical course of HIV infections in humans is highly variable between subjects. Based on the timing of progression to AIDS, HIV-infected persons can be divided into rapid progressors (which develop AIDS within 2-3 years of infection), conventional progressors (where AIDS develops between 3 and 10 years of infection), and long-term nonprogressors, or elite controllers (a rare population of HIV-infected persons that show a prolonged, spontaneous control of viral replication and tend to remain healthy). Furthermore, some persons show high levels of resistance to infection despite being exposed to the virus.\textsuperscript{80} Similarly, there is also some variability in outcome of SIV infection in macaques, with animals showing different timing of progression to AIDS despite being infected with same levels of the same virus. For example, when experimentally infected with SIVmac239, the majority of RM develop AIDS in 1 to 2 years; however, approximately 20\% of these animals progress to AIDS in < 6 months (rapid progressors), whereas < 10\% control viral replication to < 10\(^{5}\) copies of virus per milliliter of plasma and remain AIDS free for > 2 years.\textsuperscript{81,82}

It is widely accepted that the variability in the rate of progression to AIDS, as well as the susceptibility to infection, depends on a combination of host and environmental factors.\textsuperscript{80} Among host genetic determinants, several studies showed association between genes encoding chemokine receptors, their cognate ligands, or human leukocyte antigens (HLA) and the tempo of AIDS progression.

**CCR5 and RANTES**

CCR5, the key HIV/SIV entry coreceptor, is a chemokine receptor expressed on activated/effector memory T cells and macrophages. The levels of CCR5 expression may significantly impact the susceptibility to HIV infection and the clinical course of HIV infection. The more striking evidence comes from studies showing that persons carrying a 32-bp deletion in CCR5 gene, named CCR5-\Delta32, which results in a lack of CCR5 expression on the cell surface, are protected from infection if a homozygote and show a delay in progression to AIDS if a heterozygote.\textsuperscript{83-85} Expression of CCR5 on cell surface is also affected by polymorphisms on the CCR5 gene or its promoter. For example, homozygosity for CCR5-2459A, a common polymorphism, is associated with rapid progression to AIDS.\textsuperscript{86} Furthermore, AIDS progression has been associated with polymorphisms of the CCR5 ligand, regulated on activation normal T expressed and secreted (RANTES), which suppresses R5-HIV infection by reducing the amount of free, cell surface, CCR5. Specifically, 2 single nucleotide polymorphisms, \(-28G\) and \(-403A\), have been associated with increased RANTES expression and delayed progression to AIDS, whereas other RANTES polymorphism results in lower expression of RANTES and a faster disease progression.\textsuperscript{87} Polymorphisms among CCR5 have also been described in SM, leading to outgrowth of SIVsmm strains, which use noncanonical coreceptors.\textsuperscript{88}

**HLA, KIR**

Genes located within the HLA region (HLA genes) are highly important in inducing effective immune responses against invading microorganisms. The presence of specific HLA alleles and/or a marked increase in the heterogeneity of the HLA class I loci have been found to be associated with delayed progression to AIDS in HIV-infected persons. For example, HLA-B*57, HLA-B*27, and certain HLA C alleles have been reported to be consistently associated with a better control of viral replication and slower disease progression.\textsuperscript{89,90} On the other hand, expression of HLA-B*35 has been associated with accelerated progression to AIDS.\textsuperscript{91} The same feature has been documented in SIV-infected macaques, with several major histocompatibility complex class I alleles, namely, Mamu-A*01, Mamu-B*08, and Mamu-B*17, being associated with a better control of viral replication and a slower disease progression.\textsuperscript{92} This association is very strong for Mamu-B*08, with an average 50\% of SIVmac239-infected RM showing lower viral set-point and a slower progression to AIDS.\textsuperscript{93} Moreover, the diversity of HLA expression can influence disease progression with persons expressing fewer HLA alleles progressing more rapidly than persons expressing multiple HLA alleles.\textsuperscript{94}

Moreover, the activity of natural killer cells, a key component of the innate immune system capable of lysing virally infected cells, is regulated by a variety of activating and inhibitory receptors. A group of killer immunoglobulin-like receptors (KIR) participates in the complex regulation of NK-cell responses through recognition of specific HLA class I molecules on target cells. Like HLA, KIR are also highly polymorphic genetically. It has been shown that the specific combinations of the activating receptor KIR3DS1 with HLA-B alleles that encode isoleucine at position 80 (HLA-B\_Bw4-80I) increases the activity of NK cells, and it is associated with delayed progression to AIDS.\textsuperscript{95,96} In particular, this combination provides a dual protection, with a direct containment of HIV viral load and a more effective defense against certain opportunistic infections.\textsuperscript{95,96} Furthermore, elevated KIR3DS1 transcript expression, with concomitant high levels of NK cell activity, has been associated with lower risk of infection in HIV-exposed persons.\textsuperscript{97}

**TRIM5**

Tripartite motif-5\alpha isoform (TRIM5\alpha), the product of TRIM5 gene, acts as a cellular host restriction factor that mediates an early, postentry block of lentiviral replication. Specifically, it inhibits viral replication by binding and degrading the viral capsid after the virus entered into a cell.\textsuperscript{98} TRIM5\alpha plays a key role in limiting the transmission of viruses between species, with TRIM5\alpha from Old World monkeys efficiently blocking HIV, but not SIV, replication, and human TRIM5\alpha able to restrict other retroviruses, such as MLV, but unable to efficiently target HIV. In addition to its role as...
cross-species barrier for retroviruses, TRIM5α appears to be involved in controlling the replication of the host-specific virus, with polymorphisms in the B30.2/SPRY domain (that interacts with the virion capsid) being strongly associated with different ability to control viral replication in SIV-infected RM.99 Studies of TRIM5α polymorphisms in natural hosts for SIV, and antiviral effects they may exert, are certainly warranted.

Differences attributed to host species

Given that genetic predispositions can affect disease progression, it would follow that certain species of nonhuman primates would be characterized by differences in disease progression. Indeed, among Asian macaques, there are 3 species that are commonly used: cynomolgus, RM, and PTM. Among these species, it is clear that PTM progress through disease progression more quickly than the other macaque species.100 This increased disease progression rate is at least partially attributed to increased intestinal permeability, microbial translocation, and immune activation in uninfected PTM compared with uninfected RM. Hence, consideration needs to be given to which species of nonhuman primates is used for particular pathogenesis and/or vaccine studies.

In conclusion, multiple factors, acting in concert, contribute to HIV disease pathogenesis leaving infected persons profoundly immunocompromised, with a distinct and massive insult occurring during the acute phase of infection. A significant proportion of this acute insult occurs within the GI tract. Although there is some similarity between immunologic damage occurring during the acute phase of infection in natural hosts and non-natural hosts, the natural hosts are able to recover from the acute phase of infection and avoid progression to AIDS. Understanding the molecular mechanisms underlying target cell availability, down-regulation of immune activation after the acute phase of infection, differential expression of SIV and HIV receptors and coreceptors, and maintenance of immunologic function by natural hosts will lead to a better understanding of the lack of disease progression in natural hosts and to the development of novel adjunctive therapeutic interventions for HIV-infected humans. Although humans may not co-evolve with HIV such that they avoid disease progression, it is conceivable that we may limit disease progression in humans by recapitulating the immunologic phenomena observed in natural hosts.

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