Host-pathogen interaction in HIV infection

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Abstract

The host pathogen interaction is strikingly complex during HIV infection. While several immune effector mechanisms (i.e., cytotoxic T cells, neutralizing antibodies, NK cells, etc) can play a strong antiviral role in vivo, the virus is remarkably able to evade these responses. In addition, the virus preferentially infects and kills activated memory CD4+ T cells, thus exploiting the host antiviral immune response as a source of new cellular targets for infection. Recent advances in understanding (i) how HIV perturbs the host immune system, (ii) how the immune system fights HIV; and (iii) how HIV disease persists when virus replication is suppressed by antiretroviral drugs may hopefully lead to better prevention and treatment strategies for this deadly viral infection.

Introduction

Human Immunodeficiency Virus (HIV) infection, when left untreated, almost invariably results in a progressive and irreversible state of immunodeficiency (i.e., acquired immune deficiency syndrome or AIDS), whose pathogenesis is a complex phenomenon that involves numerous factors related to both the virus and the host immune system. Our understanding of HIV pathogenesis has significantly improved over the past few years, and it is hoped that these advances will soon translate in more effective interventions to prevent, treat, and hopefully cure HIV infection and AIDS. In this article, we will briefly review the most recent advances concerning how HIV infection perturbs the host immune system, how the immune system fights the virus, and how HIV disease persists when virus replication is suppressed by antiretroviral drugs.

How HIV perturbs host immune function

Many aspects of HIV/AIDS pathogenesis have been elucidated by *in vivo* studies of non-human primates infected with the Simian Immunodeficiency Virus (SIV), including both "experimental" pathogenic hosts, such as Asian macaques, and "natural" non-pathogenic hosts such as African sooty mangabeys (SMs) (1–2). HIV and SIV primarily infect activated CD4+ memory T cells expressing the main virus co-receptor CCR5, and CD4+ memory T cells are progressively depleted in both blood and mucosal tissues during pathogenic HIV/SIV infections. Of note, a recent study showed that, in naïve CD4+ T cell-deficient macaques, in which thymectomy abrogated naïve CD4+ T cell recovery after Ab-mediated

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CD4+ T cell depletion, SIV replication and CD4+ T cell dynamics post-infection are similar to control animals, thus confirming that memory CD4+ T cells are the key pathogenic players in SIV-infected macaques (3**). However, within the memory CD4+ T cell pool several subsets exist, both in terms of maturation along the axis of central, transitional, and effector memory cells, and in terms of lineage differentiation (Th1, Th2, Th17, regulatory T cells, follicular T helper cells, and possibly others) (4). A series of studies have led to the formulation of a pathogenic model (see Figure 1) in which the pattern of infected CD4+ T cells is the key determinant of HIV/SIV pathogenesis (5–11). In this view, infection of central memory CD4+ T cells (T_{CM}) is a strong correlate of pathogenesis, while infections in which T_{CM} are relatively spared (i.e., SIV-infected SMs or HIV-infected "non-progressors") are typically non-pathogenic (5–11).

The molecular mechanisms determining which CD4+ T cell subsets are predominantly infected *in vivo* remain incompletely understood. In the non-pathogenic model of SIV infection of SMs a factor protecting CD4+ T_{CM} from virus infection is the low expression of CCR5 upon activation (7). However, numerous additional host restriction factors may affect the pattern of infected cells *in vivo* (12). The family of HIV and SIV host restriction factors (HRFs) include molecules such as TRIM-5a, APOBEC-3G, BST-2/Tetherin, and various others (12). More recently it was discovered that the SAM domain HD domain-containing protein 1 (SAMHD1), a deoxynucleoside triphosphate triphosphohydrolase that restricts HIV and SIV replication by inhibiting viral DNA synthesis through depletion the intracellular dNTP pool, is the host factor counteracted by the viral protein Vpx (13–16). Intriguingly, several recent studies have shown that HRFs, including TRIM-5a (17), Tetherin (18–19), and APOBEC-3G (20), also act as innate immune sensors. Since the expression of HRFs is up-regulated in response to type I interferons, these studies define a novel and potentially important link between host restriction and innate antiviral immunity that may play a major role in determining the pattern of virus-infected cells *in vivo* during HIV and SIV infections.

While the direct role of HIV in infecting and killing CD4+ T cells is clearly central to HIV/ AIDS pathogenesis, several "indirect" mechanisms of immune deficiency have been described, including chronic immune activation and inflammation, bystander death of uninfected cells, and ineffective T cell regeneration (reviewed in 21). The pathogenic role of immune activation is confirmed by the observations that HIV-infected individuals with undetectable viremia but significant immune activation can progress to AIDS (22) and that individuals with preserved CD4+ T cell counts despite persistently high viremia (i.e., viremic non-progressors) show limited immune activation (23–24). Interestingly, systemic immune activation is also a possible determinant of viral acquisition if present prior to infection (25–28). An additional important feature of pathogenic SIV/HIV infections is the functional and structural impairment of lymph nodes due to (i) virus trapping in follicular dendritic cells and virus replication in CD4+ follicular T helper cells (*8, 29, *30, *31), (ii) disruption of the fibroblastic reticular network, with increased collagen deposition (32), and (iii) failure of CD4+ T cell homeostasis (32). In SIV-infected macaques, the structural impairment of lymph nodes can be partially restored by the administration of TNF antagonists during the acute phase of infection (33). An additional hallmark of HIV/AIDS pathogenesis is the loss of mucosal immune integrity with consequent translocation of microbial products from the intestinal lumen to the portal and systemic circulation, where they cause persistent innate immune activation (34). Recent advances in this area include the observations that pathogenic SIV infection is associated with major changes in the intestinal virome (35) and that probiotic/prebiotic supplementation of antiretroviral treatment improves the gastrointestinal immunity in SIV-infected macaques (**36).

How the immune system fights HIV

Several components of the host immune system can suppress virus replication *in vivo*, including CD8+ T cells, CD4+ T cells, NK cells, neutralizing antibodies, and possibly other mechanisms as well. In the case of CD4+ T cells, the recent characterization of potential direct antiviral effects (37,38) underscores the complex pathophysiologic role of these cells that, when activated, also serve as key targets for the virus (39). As for the CD8+ T cells, their role is well characterized in terms of both benefit, as mediators of the "elite controller" phenotype, and limitations as shown by virus CTL epitope escape and insufficient efficacy when induced by candidate AIDS vaccines (reviewed in 40). The main recent advances in this area are the observations that (i) the protection conferred by live-attenuated SIV vaccines is mediated by activated effector memory CD8+ T cells in lymph nodes that can suppress or even completely contain early SIV replication at these sites (*41); (ii) rhesus cytomegalovirus (rCMV)-based vectors expressing SIV antigens confer strong protection from highly pathogenic challenge through the persistent induction of effector CD8+ T cells in mucosal tissues (**42); and (iii) macaques expressing "protective" MHC class I alleles (a model for HIV elite controllers) that were immunized against the appropriately MHC-restricted Nef and Vif epitopes potently suppressed virus replication after pathogenic SIV challenge (*43). Collectively, these elegant studies in non-human primates directly demonstrated the potential of antiviral CD8$^+$ T cell responses and how this antiviral activity takes different flavors based on the vector used to elicit these responses as well as the host genetic background. Whether similar responses can be elicited in humans by specific immunogens used as candidate AIDS vaccines remains to be determined.

Perhaps the most striking recent advances in our understanding of HIV-specific immune responses are in the area of HIV-specific neutralizing antibodies. A series of breakthrough studies conducted independently in several laboratories have shown that a substantial portion of HIV-infected individuals produce very potent and broadly reactive neutralizing antibodies (bnAbs) (44–50). In addition, these studies revealed the key targets for neutralization in the HIV Envelope protein (i.e., CD4 binding sites, the so-called membrane-proximal external region or MPER, and the N-linked glycans in positions N160 and N332), and some previously unrecognized structural and genetic features of these bnAbs (i.e., long complementary determining region-H3 with ~30 aminoacids, high rate of somatic mutation, and the presence of genetic insertions or deletions) (44–50). Intriguingly, the "germline" versions of a subset of these bnABs (i.e., those directed against the CD4 binding site) do not seem to recognize HIV Envelope proteins (**51), therefore suggesting that a complex, multi-step process of sequential antigenic stimulation of the relevant B cell clones is required. Following viral and antibody evolution from early stages of infection up to the point of bnAb development may provide valuable insight into the interplay between antibody lineage development and viral evolution. A recent study by Liao et al showed that the CH103 CD4-binding site bnAb develops relatively early in infection and that the "unmutated" common ancestor of CH103 avidly binds the transmitted/founder virus (52). However, increased neutralizing breadth occurs after significant diversification of viral variants and the induction of further mutations in CH103 lineage antibodies. In another study, Moore et al. elucidate the case of two HIV-infected individuals wherein the transmitted/founder virus develops an escape mutation resulting in a glycan-shift from Asn 334 to Asn 332 on the viral envelope, thus inducing PGT128-like glycan-dependent bnAbs in these individuals (53). These reports provides evidence that viral evolution within the infected host facilitates development of bnAbs. Of note, Moore et al. also found that while the conserved viral epitope for glycan-dependent bnAB arises quite frequently in HIV-infected individuals, this does not guarantee the development of the bnAb in that individual.

The naturally occurring bnAbs, in most cases, are produced several years after the initial infection and in the context of chronic virus replication, which they are incapable of suppressing likely due to escape mechanisms. However, passive transfer experiments in macaques have convincingly demonstrated that HIV-specific bnAbs can provide complete protection against transmission of chimeric SHIVs expressing the HIV-1 envelope glycoprotein (54,55). These experiments strongly suggest that a vaccine designed to elicit and to maintain such antibodies would protect against HIV-1. Most recently, Moldt et al. demonstrated that PGT121, one of the most potent bnAbs identified so far, provides sterilizing immunity to macaques against high-dose mucosal SHIV challenge after passive administration of only 1 mg/kg of the Ab, thus at lower dose than previously observed (56). Further elucidation of the genetic, structural, and functional properties of these naturally occurring bnAbs provides essential information to be used for the rational design of novel and more effective immunogens. In an attempt to design envelope-based immunogens capable of specifically and robustly inducing potent bnAbs, Jardine et al. have used computation-guided *in vitro* screening to engineer a gp120 outer domain immunogen that can activate both germline and mature VRC01-class B cells thus providing a promising immunogen to be tested in preclinical macaque studies (57).

In parallel to this progress, there has been significant recent advance in understanding the role of follicular T helper cells (T_{FH}) as both helpers for HIV-specific antibody responses and targets for virus infection. A series of important studies in both HIV-infected humans and SIV-infected macaques have independently shown that while T_{FH} are a preferential target for direct virus infection they are not depleted as compared to other memory CD4+ T cell subsets (8, 29 *30, *31, *58). Recently, Cubas et al. showed that ligation of PD1 on T_{FH} cells reduces IL-21 production and ICOS expression, suggesting an impaired ability of T_{FH} cells to provide "help" to germinal center B cells in chronic stages of HIV infection (59). The full extent to which T_{FH} contribute to the generation of HIV-specific bnABs-- in the context of either natural infection of immunization of uninfected individuals-- is the object of intense investigation.

Pathogenic HIV/SIV infections are associated with vigorous innate immune responses that result in high production of type I interferons (IFN-I) and persistent upregulation of interferon stimulated genes (ISGs) (60–63). These studies have emphasized the spectacular dichotomy of IFN-I signaling in AIDS pathogenesis, in which IFN-dependent HRFs (i.e., TRIM5a, Tetherin, APOBECs, SAMHD1, TREX etc) act as potent antiviral effectors and, at the same time, chronic IFN-I signaling has been associated with both HIV/SIV-disease progression and poor immunological response to ART (60–64). In a recent study, IFN was administered to SIV-infected sooty mangabeys, in which low immune activation is associated with transient ISG up-regulation, resulting in decreased virus replication and no signs of accelerated disease progression (65). This study emphasized the *in vivo* antiviral effect of IFNs and supported the possibility that this effect may be exploited in the clinical setting of ART-treated HIV-infected individuals (66–68).

Host-pathogen interaction in the age of ART

An increasingly high percentage of HIV-infected individuals receive antiretroviral therapy (ART) that is capable of fully suppressing virus replication for prolonged periods of time. While ART results in a dramatic reduction of HIV-associated morbidity and mortality, the currently available treatments do not eradicate the infection nor achieve a full recovery from the immune dysfunction induced by the virus (68). In fact, many studies have shown that residual immune activation and/or incomplete immune reconstitution occur, at various levels of severity, in virtually all ART-treated HIV-infected individuals, and are involved in the development of the so-called "end-organ disease" which includes cardiovascular disease,

HIV-associated neurocognitive dysfunction, metabolic and kidney abnormalities, bone disease, and others (reviewed in 69). Elucidating the exact cellular and molecular mechanisms responsible for this end organ disease will be essential to design intervention to use, in addition to standard ART, in the clinical management of HIV-infected individuals. The potential mechanisms that have been proposed include low level virus replication; disruption of lymphoid tissue architecture; persistent mucosal immune dysfunction and microbial translocation; residual innate immune activation via the TLR7/9-type I IFN pathway; ineffective homeostatic signals; activation of atherogenic pathways; and persistent replication of CMV (69). Importantly, initial studies aimed at reverting these mechanisms with specific pharmacological interventions are showing some promise (**36, 70–71). Whether and to what extent some residual virus replication contributes to the persistent HIV-related morbidity under ART is unclear. On the other hand, a full suppression of virus replication would be necessary to achieve a "functional cure" for HIV infection, which is defined as undetectable viremia in absence of ART, lack of measurable immunological abnormalities, and projected lifespan comparable to age-matched HIV-uninfected individuals. A key obstacle in this regard is the presence of persistent reservoirs of latently infected cells that are able, in most cases, to reinstate high-level virus replication soon after ART interruption (68). Several studies suggested that resting memory CD4+ T cells (and, in particular, central memory CD4+ T cells) are the main contributors to this reservoir (reviewed in 72), consistent with the key role of these cells in the natural history of HIV pathogenesis (5–11). Potential approaches targeting this CD4+ T_{CM} reservoir include inducing the reactivation of latent virus, permanent silencing of latent integrated provirus, promoting the differentiation of T_{CM} into shorter lived cells, boosting of cellular antiviral immune responses, treating the residual immune activation with immunomodulatory agents, and eliminating the reservoirs with replacement by uninfected cells through a combination of lymphoablation and gene and/or stem cell therapy (68, 72). However, any such approach appears unlikely to succeed unless it takes into full account the complex biology of CD4+ T cell subsets, and how this biology may influence the mechanisms by which the persistent reservoirs are established and maintained under ART.

Conclusions

The host-pathogen interaction during HIV infection is peculiarly complex due to the fact that the virus infects immune cells, and that antiviral immune responses end up paradoxically favoring virus replication through the creation of cellular targets for infection. Several aspects of this complex interaction have been clarified, and with further progress it is reasonable to hope that a vaccine and a cure for this deadly infection will emerge in the not so distant future.

Acknowledgments

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Highlights

- Pattern of virus-infected CD4+ T cells as a key factor in HIV/AIDS pathogenesis.

- Novel properties of antiviral CTL responses described in macaques.

- Immunogens to elicit HIV-specific bnAbs as key to developing an AIDS vaccine.

- Viral reservoir clearance under ART as the way to "cure" HIV infection..
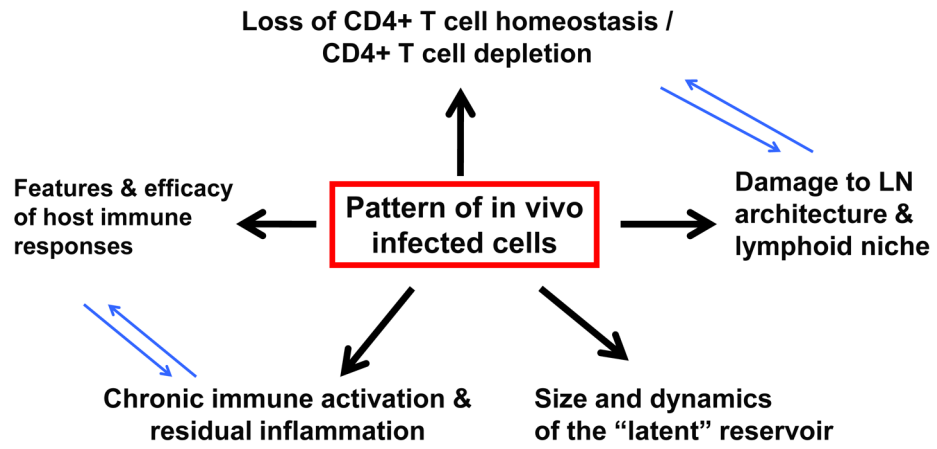
Figure 1.
Te pattern of virus-infected cells in vivo influences many aspects of HIV/AIDS pathogenesis.