Immunopathogenesis of AIDS

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Twenty-five years after the discovery of HIV as the cause of AIDS, tremendous progress has been made in reducing the morbidity and mortality associated with this disease. However, there is still neither a cure nor a vaccine for HIV infection. This shortcoming is likely a consequence of our incomplete understanding of the mechanisms of AIDS pathogenesis, particularly with regard to the interaction between the virus and the host immune system. In this article we review a series of recent advances in specific areas of HIV immunopathogenesis research: virus–host cell interactions; immune responses to HIV; chronic immune activation; and natural simian immunodeficiency virus infections. Finally, we discuss the potential implications of these findings for HIV/AIDS therapy and vaccines.

Introduction

Primate lentiviral infections, including HIV infection of humans and simian immunodeficiency virus (SIV) of numerous nonhuman primate species, are characterized by a complex and highly dynamic interaction between the virus and the host immune system. This interaction ultimately leads to a severe state of immunodeficiency, AIDS, in humans and macaques (which are recent and experimental hosts for HIV and SIV infections), but does not result in disease in more than 40 African nonhuman primates naturally infected with SIV, such as sooty mangabeys, African green monkeys, and mandrills. The interaction between primate lentiviruses and host immune systems has at least four main aspects that profoundly influence AIDS immunopathogenesis and thus continue to be the focus of intense research: 1) these viruses replicate in immune cells (ie, activated CD4⁺ T cells and macrophages); 2) the immune response to these viruses appears to suppress virus replication somewhat (via antiviral neutralizing antibodies and CD8⁺ T-cell-mediated antiviral immune responses) while

also paradoxically favoring virus replication by increasing the number of available target cells; 3) these viruses have a tremendous ability to escape host immune responses due to the peculiar molecular structure of their envelope proteins, tremendous genetic variability and flexibility, and various active immune evasion strategies; and 4) in the absence of effective immune control, the presence of chronic, generalized immune activation becomes a factor associated with (and likely leading to) progression to AIDS. Because of this complexity, the representation of HIV/AIDS pathogenesis has shifted from models that are mainly focused on the cytopathic role of the virus (ie, its direct killing of infected cells) to more comprehensive models that encompass the complexity of the virus–immune system interaction (immunopathogenesis) and incorporate chronic immune activation as a key factor for disease progression. In this review, we summarize the most recent advances in HIV/AIDS immunology and immunopathogenesis.

Virus–Host Cell Interaction

A series of important discoveries made over the past few years clarified some previously poorly understood aspects of the molecular interactions between primate lentiviruses and host cells. Perhaps the two most important recent advances were the description of the cytoplasmic body molecule TRIM5a as a key post-entry, pre-integration, cellular restriction factor that acts through inhibition of virion uncoating, and the discovery of the cellular cytidine deaminase APO-BEC3G [1,2]. Vif mediates the degradation of APOBEC3G, which is otherwise incorporated into progeny virions and leads to lethal hypermutation of the viral genome upon infection of the new target cell. More recently, the complexity of the interaction between HIV and cellular factors was further emphasized in a study describing the results of a functional genomic screening using a large library of short interfering RNA (siRNA). This work allowed the identification of a large set of cellular genes whose expression is required for effective virus replication [3]. Although using a somewhat artificial experimental system (ie, HeLa-derived cells that are not the natural host for HIV), these findings provide a previously unknown estimate for the number of individual virus–host cell factors interactions occurring during productive HIV infection.

In recent months, another major breakthrough in this field was the discovery that the cellular protein CD317/tetherin/BST-2 prevents the release of virions from the surface of infected cells [4••,5••]. In turn, the effect of

CD317/tetherin is inhibited by the virus protein Vpu (for HIV-1) or by the intracytoplasmic tail of Env (for HIV-2 and certain SIVs). This antiviral effect of CD317 has profound and intriguing implications for viral pathogenesis and generation of immune responses to HIV. CD317 is a type 1 interferon (IFN)-induced surface protein that has a peculiar structure characterized by a transmembrane domain as well as a glycosylphosphatidylinositol anchor domain. This structure makes CD317 particularly well suited to tether (hence, “tetherin”) budding virions to the surface of cells. It remains to be addressed whether, and if so, how, the CD317/tetherin antiviral activity is synergistic with the function of the calcium-modulating cyclophilin ligand (CAML) protein, another recently identified Vpu-interacting host cell factor that restricts HIV-1 release using an unknown mechanism [6]. From an immunologic point of view, it will be interesting to determine if CD317 is involved in the trapping of virions by dendritic cells (DCs) and the resulting enhanced transmission of HIV/SIV to activated CD4⁺ T cells. CD317/tetherin may also play an important role in priming antigen-presenting cells (including DCs) and thus influence the type of adaptive immune response to HIV. Interestingly, a strong direct antiviral role of another type 1 IFN-induced protein, TRIM-22, was described, further emphasizing the importance of type 1 IFN-mediated innate responses in inhibiting HIV replication [7]. In all, these exciting findings provide a continually more accurate view of the viral life cycle and its interaction with cellular proteins that will eventually translate into the identification of new targets for antiviral therapy.

Immune Responses to HIV/SIV

Pathogenic HIV/SIV infections are typically associated with strong, readily detectable, and persistent virus-specific adaptive immune responses involving B cells (through the production of virus-specific antibodies) and T cells. Unfortunately, these immune responses almost invariably fail to control virus replication and thus do not protect from disease progression. The reasons behind this failure are complex, and include 1) the ability of the virus to mutate and escape immune responses; 2) the structure of the envelope protein, which allows the virus to avoid antibody-mediated neutralization; 3) the ability of some HIV/SIV gene products, in particular Nef, to interfere with antigen presentation; 4) the presence of a pool of immunologically “silent,” latently infected cells; and 5) the fact that virus-specific CD4⁺ T-helper cells are preferentially targeted by the virus. The enormous task that the immune system confronts in trying to prevent lentiviral infection and/or contain virus replication after infection was recently emphasized by the much-publicized negative result of the first large-scale, phase 2b, clinical trial of a T-cell-based candidate AIDS vaccine (human adenovirus type 5 expressing HIV gag/nef/pol—the STEP trial, also known as the Merck V520-023 study) [8]. Of

interest, significant advances have defined new mechanisms underlying the failure of the immune system to control HIV infection. For instance, it was proposed that the increased expression of certain “inhibitory” surface markers (ie, programmed death 1, PD-1 and cytotoxic T-lymphocyte antigen 4, CTLA-4) on the surface of T cells during chronic HIV infection is a strong correlate of the loss of control of virus replication and disease progression [9–14]. HIV-specific T-cell function can be partially restored *in vitro* when these inhibitory signals are blocked, and thus it was proposed that *in vivo* PD-1 and/or CTLA-4 blockade may reenergize the exhausted immune system and result in better control of virus replication. It remains to be determined, however, whether and to what extent the expression of PD-1 and CTLA-4 causes, rather than reflects, HIV/SIV-associated T-cell dysfunction. As such, the possibility that blocking inhibitory signals on CD4⁺ T cells could result in the increased availability of target cells for the virus must be considered [15–17]. Furthermore, a recent study in SIV-infected sooty mangabeys revealed that increased PD-1 expression is temporally associated with increased expression of immune activation markers during acute infection and that the resolution of this acute activation is accompanied by PD-1 down-regulation [18].

An area of research that is crucial for the design of an effective HIV/AIDS vaccine is the identification of immunologic correlates of protection from virus replication and disease progression. Studies of HIV-infected humans or SIV-infected macaques that spontaneously and persistently suppress virus replication below detectable limits (elite controllers, EC) may potentially provide important insights. However, it is still unclear to what extent the EC phenotype is caused by strong immune responses to HIV/SIV as opposed to low virus fitness and/or specific host genetic factors (ie, CCR5 genotype, CCL3L1 copy number). This complexity was emphasized by a recent report that failed to identify clear correlates of immune protection in a large group of EC SIV-infected rhesus macaques that carried the protective Mamu-B*08 and B*17 major histocompatibility complex (MHC) class 1 alleles [19]. Even more provocative is the suggestion that control of viremia itself is not sufficient to avoid CD4⁺ T-cell depletion and progression to AIDS in a subset of ECs [20••]. In this context, one major but often ignored problem is that it is still largely unknown what proteins of HIV/SIV are targeted by cytotoxic T lymphocyte (CTL) responses early enough to elicit an effective block of virus replication at the level of the individual infected cell. Sacha et al. [21•] recently used an elegant *in vitro* experimental system to address this issue. In this study, these authors showed that HIV Gag protein may be the best target for CTLs because it can be recognized on infected cells in the context of MHC class 1 molecules before HIV integration and *de novo* viral protein expression. More recently, the same authors discovered that even within the same HIV antigen (ie, Gag) there is a priority of presentation among individual epitopes [22]. The importance of Gag as a target for protective CTL responses was

Table 1. Causes of immune activation

Study	Type of activation
	Direct
Kiepiela et al. [23], Betts et al. [24], Manuel et al. [25], Almeida et al. [26]	T-cell recognition of HIV epitopes—adaptive immune response
Funderburg et al. [34], Meier et al. [35]	TLR stimulus in response to HIV infection—innate immune response
Arthos et al. [33]	Envelope-mediated signaling through $\alpha 4\beta 7$ -integrin Loss of T-regulatory cells
	Indirect
Brenchley et al. [36], Ancuta et al. [37], Raffatellu et al. [38]	Microbial translocation across weakened mucosal barrier
Mueller et al. [16]	Cytokine production (IL-2, IL-7, IL-15)
Gottlieb et al. [29]	Opportunistic infections
Maness et al. [19], Hunt et al. [20••], Grossman et al. [30], Okoye et al. [42••]	Homeostatic proliferation in response to CD4 ⁺ T-cell depletion
IL—interleukin; TLR—Toll-like receptor.	

also suggested by a study reporting a significant correlation between Gag-specific CTL responses and viral load (as well as an inverse correlation between Env-specific responses and viremia) in a large cohort of HIV-infected individuals from South Africa [23]. Clearly, the field of HIV immunology remains haunted by a basic chicken-and-egg issue: are the ostensibly better immune responses observed in association with low viral load causing this EC phenotype or, alternatively, does preservation of the immune system due to other factors make these HIV-specific T-cell responses appear to be more effective? It is, however, becoming apparent that a combination of multifunctionality, high avidity, increased clonal turnover, and Gag-focused responses may capture the key features of CTL responses associated with a more benign course of infection [24–26].

Given our incomplete understanding of the antiviral role of CTL responses during HIV/SIV infections, substantial research efforts have been devoted to the study of other cell types, such as natural killer (NK) cells, macrophages, and γ - δ T cells. Of interest, it was shown that certain combinations of NK cell receptors from the *KIR3DL* locus with HLA-B subtypes, particularly the activating KIR3DS1 receptor with its presumed ligand HLA-Bw4, have been associated with strong antiviral effects in vitro and slow progression to AIDS in epidemiologic studies [27,28].

Chronic Immune Activation

The somewhat paradoxical observation that the clinically devastating immunodeficiency following HIV infection occurs in the context of major immune system activation was made in the very first description of AIDS [29]. Over the past few years, many observations led to the formulation of AIDS pathogenesis models in which HIV-associated chronic, generalized immune activation plays a central role in disrupting immune system homeostasis

[30–32]. More recently, significant advances were made in addressing two central questions in this area of research: 1) what causes HIV/SIV-associated immune activation? and 2) why is this immune activation so disruptive to immune homeostasis?

The mechanisms underlying HIV-associated immune activation are very complex and include 1) direct effects by the virus and its gene products (eg, Env, Tat); 2) innate and adaptive immune responses to viral antigens; 3) immune responses to secondary antigens, including opportunistic pathogens (eg, Epstein-Barr virus, cytomegalovirus, *Candida albicans*); 4) bystander immune activation induced by cytokines and other factors; 5) the failure of immunoregulatory circuits (ie, T-regulatory cells); and 6) a response to the translocation of microbes from the intestinal lumen into the systemic circulation [32] (Table 1). A potential role for HIV in directly inducing immune activation was proposed to result from the previously unrecognized ability of HIV Env to bind to the adhesion molecule $\alpha 4\beta 7$ -integrin [33]. Intriguingly, this effect of Env would not be limited to CD4⁺ T cells but would also involve CD8⁺ T cells, which are known to be hyperactivated during HIV infection. The ability of HIV to activate large numbers of T cells in vivo has long puzzled scientists. Recent work conducted in the laboratories of Altfeld and Lederman may provide an explanation for this T-cell hyperactivation. These groups described how HIV can activate large numbers of T cells following stimulation of DCs via binding to various Toll-like receptors (TLR) [34,35]. In particular, it was shown that the single-stranded RNA of HIV-1 encodes multiple uridine-rich regions that act functionally as TLR-7/8 ligands on plasmacytoid dendritic cells [35]. Although the sequence of events involving innate and adaptive immune activation is still poorly defined, it is becoming clear that HIV and SIV infections may lead to stimulation of T cells (including those that are specific for other antigens) by unconventional mechanisms—distinct from the direct, T-cell receptor

Figure 1. Chronic immune activation and the progression to immune exhaustion. HIV infection of activated CD4⁺ T cells leads to the expansion of CD8⁺ effector T cells (CTLs) specific for the originally acquired virus. CD4⁺ T-cell depletion occurs as a result of virus-mediated cytopathicity, CTL-mediated cytolysis, and bystander immune activation and apoptosis. CD4⁺ T cells proliferate and become increasingly activated (as described in Table 1), heightening their susceptibility to viral infection. As mutations accrue within the host's virus populations, CTL responses lose the ability to effectively combat the majority of virions, and new responses must be generated, perpetuating the cycle of immune activation and ongoing CD4⁺ T-cell depletion. Over many years, the ability to generate and expand new CD4⁺ and CD8⁺ T cells declines, accelerating the progression to AIDS.

(TCR)-mediated recognition of HIV/SIV antigens. Microbial translocation from the intestinal lumen to the systemic circulation is a well-recognized cause of immune activation and disease progression during pathogenic HIV/SIV infections [36]. The importance of this phenomenon was recently emphasized in an article suggesting a link between microbial translocation and neuropathogenesis via increased transport of HIV to the central nervous system by activated macrophages [37]. Subsequently, a series of studies conducted independently by various laboratories suggested a key role for the newly described subset of CD4⁺ T cells—Th17 cells—in the immunopathogenesis of AIDS [38–40]. Th17 cells are defined based on the production of cytokines such as IL-17 and IL-22 as well as their homing to mucosa-associated lymphoid tissues (MALT), where they mediate strong antimicrobial immunity [41]. During pathogenic HIV/SIV infections, CD4⁺ Th17 cells are preferentially depleted in the MALT (but not blood) of infected individuals, thus providing a potential new pathogenic

mechanism for the HIV-associated mucosal immune dysfunction that leads to microbial translocation and chronic immune activation.

Significant progress has also been made in understanding how chronic immune activation negatively affects the preservation of the CD4⁺ T-cell pool to ultimately cause progression to AIDS (Fig. 1). In an elegant set of experiments performed in the laboratory of Louis Picker, it was shown that in chronically SIV-infected rhesus macaques, the key marker of disease progression is the depletion of central memory CD4⁺ T cells [42••]. This observation showed for the first time that although effector memory CD4⁺ T cells are the main target of the virus (and thus the cell population that is most immediately affected by SIV replication), progression to AIDS is largely determined by the destruction, failing production, and gradual decline of central memory CD4⁺ T cells. In another intriguing study, the preservation of the central memory T-cell pool was correlated, in a subset of EC HIV-infected individuals, with the inactivation of the

FOXO3a intracellular signaling pathway [43•]. Collectively, these studies identify new biologic links between the abnormal activation of CD4⁺ T cells (particularly those of central memory cells) and the overall demise of the CD4⁺ T-cell pool during HIV/SIV infection. The potential dangers of increasing immune activation while conducting interventions aimed at enhancing the immune responses to HIV/SIV have been predominantly emphasized by studies in which interleukin-15 or an anti-CTLA-4 were administered to SIV-infected rhesus macaques [15–17]. In both instances, treatment may result in increasing virus replication (most likely due to increased availability of target cells) and consequent accelerated course of disease. An important implication of these studies is that they emphasize the potential pitfalls of interventions aimed at reversing *in vivo* the HIV-associated immune dysfunction by manipulating inhibitory receptors.

Natural SIV Infection

In stark contrast to the pathogenic HIV infection of humans and SIV infection of macaques, SIV infection in its natural hosts—African nonhuman primates, such as sooty mangabeys, African green monkeys, and mandrills—is typically nonpathogenic, with the hosts living an apparently normal lifespan after becoming infected [32]. It is increasingly recognized that understanding the mechanisms responsible for the AIDS resistance of natural SIV hosts will provide important insights regarding the pathogenesis of HIV infection and AIDS. Several early studies showed that natural SIV hosts remain asymptomatic and preserve healthy levels of CD4⁺ T cells despite persistently high levels of virus replication. Another peculiar feature of natural SIV infections is that they appear to be consistently associated with low levels of immune activation. Recent studies have significantly advanced this field by showing that natural SIV infection has an impact on CD4⁺ T-cell homeostasis and by elucidating some of the causes underlying the immune attenuated profile of natural SIV hosts.

Two articles reporting experiments conducted in sooty mangabeys and African green monkeys showed that acute SIV infection in these “nonprogressive” hosts is similar to pathogenic HIV/SIV infections in that it is also associated with rapid and severe depletion of mucosal CD4⁺ T cells [44,45]. That natural SIV infections are not necessarily silent immunologically was further confirmed by the observation that profound systemic CD4⁺ T-cell depletion is observed in a subset of SIV-infected sooty mangabeys [46,47]. These CD4-low, SIV-infected sooty mangabeys do not show any signs of AIDS, suggesting that in this species, CD4⁺ T cells are more dispensable and/or that immune activation is a *sine qua non* for disease progression during primate lentiviral infections. Of additional interest, in sooty mangabeys and African green monkeys infected with SIV, the average *in vivo* lifespan of infected cells is similar to that observed in pathogenic HIV/SIV infections [48,49]. This finding strongly suggests that the relatively

benign course of SIV infection in natural hosts is not due to lower intrinsic cytopathicity by the virus. Previous studies of SIV-specific T-cell responses in sooty mangabeys also indicated that the AIDS resistance of these animals is highly unlikely to be related to better immune control of virus replication [50]. Collectively, these reports emphasize that the apathogenicity of natural SIV infections cannot be explained simply by lower virus replication, reduced CD4⁺ T-cell destruction, and/or better immune responses, but requires a further understanding of the specific dynamics of the host–virus interaction in these species.

Several current studies focus intently on the mechanisms by which natural SIV hosts consistently avoid chronic immune activation. These mechanisms are clearly complex and may vary widely across different monkey species. A few common themes have recently emerged, however, including the absence of microbial translocation [36], a decreased type 1 IFN response to TLR ligands by plasmacytoid DCs [51,52], the ability of SIV Nef to down-modulate CD3-TCR [53,54], and the presence of lower levels of CCR5 on CD4⁺ T cells [55]. This last observation is of interest because it is consistent with a model wherein reduced CCR5 expression protects hosts from HIV disease progression independent of the role of CCR5 as a coreceptor for virus entry [56•,57]. Although we are still far from a complete understanding of why natural SIV infections are nonpathogenic, it is likely that further advances in this area of research will continue to provide useful clues to the mechanisms of AIDS pathogenesis in HIV-infected humans.

Conclusions

In this article we summarized a series of key advances made over the past few years in understanding HIV immunopathogenesis. Many of these findings are of particular interest because of their implications for HIV therapy and vaccines. The substantial improvement in understanding the molecular interaction between HIV/SIV and host cells may define new targets for antiviral therapy. Drugs that disrupt the virus–cell interactions required for HIV replication by acting on a particular cellular protein may represent an interesting new class of antiviral agents for which the mutability of the virus may not be a serious limiting factor. Our growing body of knowledge about the pathogenic role of chronic immune activation in determining HIV/SIV disease progression suggests that scientists in the field should more critically investigate the potential beneficial effects of interventions aimed at blunting chronic immune activation. These interventions may prove particularly useful in accelerating the recovery of immune function (by restoring and/or rebalancing the CD4⁺ T-cell pool), especially once virus replication has been successfully suppressed using conventional antiretroviral drugs. In terms of HIV/AIDS vaccine development, the key message emerging from the most recent studies is that much more needs to be learned about the interaction

between HIV and the host immune system before we can reasonably expect to have a safe and effective AIDS vaccine. Although perhaps sobering, this message suggests that the optimal use of the available resources may require more emphasis on basic discovery and less emphasis on initiating clinical trials for candidate AIDS vaccines that have little to no chance of succeeding.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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