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Non-Human Primate Models in AIDS Research

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Abstract

Purpose of review—Over the past decades, AIDS research has made tremendous progress in all key areas, including pathogenesis, prevention, and treatment. In particular, the introduction of potent antiretroviral therapy (ART) has dramatically reduced the morbidity and mortality of HIV-infected individuals. On the other hand, several challenges remain, including the absence of a vaccine that can reliably prevent virus acquisition, and the inability of current ART regimens to eradicate the infection.

Recent findings—A number of key advances in HIV/AIDS research have been made possible by the extensive use of animal models, and in particular the non-human primate models of SIV and SHIV infection of various monkey species, including macaques, sooty mangabeys, vervets, and others. Key advantages of these models include the ability to control for parameters that are virtually impossible to assess in humans, to extensively study cells and tissues (including elective necropsy), and to perform proof-of-concept studies that would pose unacceptable safety risks in humans.

Summary—In this review, we describe the most recent advances in the use of animal models for HIV/AIDS research, and will break down these advances in three areas: (i) models for virus transmission, dissemination, and pathogenesis; (ii) models for virus prevention and vaccines; and (iii) models for virus eradication and indefinite virus containment (functional cure) under ART.

Keywords

SIV; non-human primates; animal models

Introduction

Animal models that have been used for HIV/AIDS research include HIV-1 infection of chimpanzees, which has been largely abandoned for ethical and logistical reasons, SIV infection of numerous species of monkeys, and various models of humanized mice [1]. In this review we will mainly focus on the pathogenic models of simian immunodeficiency

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virus (SIV) and simian-human immunodeficiency virus (SHIV) infections of Asian macaques, which have facilitated many important advances in understanding the biology of HIV infection in humans (Table 1). The so-called “natural” SIV infections of African monkey species such as sooty mangabeys and African green monkeys-- which are typically non-pathogenic despite relatively high levels of viremia-- are discussed in greater detail in another recent review [2].

The unquestionable utility of the SIV/macaque model for AIDS research is related to the fact that macaques are physiologically and immunologically similar to humans, thus representing a significant advantage over rodents and other species. In addition, pathogenic SIV infection of macaques leads to a disease called “simian AIDS” that is similar in many respect to the disease caused by HIV-1 in humans [1]. From a methodological point of view, the main advantage of the macaque model is that it allows for a number of experimental interventions (i.e., intensive tissue sampling; immunological manipulations; “risky” preventive or therapeutic approaches) that cannot be conducted in humans. These interventions have provided, and continue to provide, essential information to reach a deeper mechanistic understanding of the biology of HIV infection and AIDS.

It should be noted that there are numerous models of pathogenic SIV infection, based on the macaque species (rhesus, pigtail, cynomolgus, etc) and the used virus (SIVmac, SIVsm, SHIVs, etc). In addition, the rapidly progressing genetic characterization of these animals (MHC and TRIM5 alleles, availability of full genome sequences, etc) allowed for the development of many “sub-models” that may be uniquely appropriate to address a specific scientific question. Of course these models have limitations-- like any existing animal model for any human disease-- as monkeys are not humans and SIVs are different from HIV-1. On the other hand, the biological similarities between human and simian AIDS (see Table 2) are such that many consider the SIV/macaque model the most useful animal model ever developed in biomedical research.

Non-human primate models for HIV transmission and pathogenesis

Non-human primates have distinct advantages over human subjects for investigating the earliest stages of lentivirus infection in terms of the ability to control the timing, dose and route of virus inoculation, as well as collecting samples from tissues that for ethical and logistical reasons are difficult to collect from humans (e.g. vaginal and rectal mucosa, inguinal lymph nodes). Macaques can be infected with SIV, or simian-human immunodeficiency virus (SHIV) chimeric viruses, by vaginal or rectal routes to model sexual transmission of HIV-1, or by oral inoculation to model mother-to-child breast milk transmission. Single-genome amplification and sequence analysis of early-transmitted founder viruses have revealed that vaginal and rectal transmission of SIV in macaques is dose-dependent, and at low challenge doses, the number of transmitted/founder viruses is small, often representing only a single inoculum variant [3-4]. As such, the model recapitulates the bottleneck that typically results in the sexual transmission of a single founder virus in most HIV-infected individuals [5-6]. Because of these similarities, macaques have been used extensively for pre-clinical studies to test various microbicides and vaccines for mucosal protection against HIV acquisition. Repeated low-dose vaginal

and rectal challenge models have been used to mimic sexual transmission of HIV-1 [7-8]. These models more accurately reflect natural routes and doses of HIV-1 exposure, and allow for comparisons of per-exposure rates of infection as an additional measure of the outcome of challenge. However, they pose significant practical challenges, including the need for greater numbers of animals to achieve sufficient statistical power, the potentially confounding variable of failure to infect all control animals, and more protracted, expensive, and labor-intensive challenge regimens. Vaginal challenge models are also complicated by menstrual cycle variation in the thickness of the vaginal epithelium, which can affect the efficiency of virus transmission. Treatment with Depo-Provera, a progesterone-based contraceptive that thins the vaginal epithelium, can be used to control for this variation. However, the physiological relevance of protection against vaginal SIV/SHIV transmission in Depo-Provera-treated animals is controversial [9].

The use of NHP models for studies of AIDS pathogenesis generated many results that have profoundly influenced this field of research over the past few years. Comprehensive comparative studies of the pathogenic SIV/SHIV infections of Asian macaques and the non-pathogenic SIV infections of African natural hosts (i.e., sooty mangabeys, SMs, African green monkeys, AGMs, and others) have shown that the level of virus replication measured as viral copies/ml of plasma is not the only determinant of disease progression, and that a key role is played by factors such as the chronic immune activation and the pattern of virus infection in different CD4+ T cell subsets (reviewed in [2]). The observation that non-pathogenic SIV infections are associated with relatively low levels of infection in central-memory CD4+ T cells (T_{CM}) and in the lymph nodes provided essential support to the concept that CD4+ T_{CM} failure is the key pathogenic process underlying the immune deficiency that follows HIV infection [10, 11*]. Recently, a model of naïve CD4+ T cell-deficient macaques, in which thymectomy abrogates naïve CD4+ T cell recovery after Ab-mediated CD4+ T cell depletion, has been developed in the Picker's lab [12**]. This model indicated that naive CD4+ T cell deficient animals display SIV replication and CD4+ T cell dynamics similar to control animals, thus suggesting that naive CD4+ T cells are indeed dispensable for memory CD4+ T cell homeostasis during pathogenic SIV infection of macaques [12**]. An additional distinct feature of pathogenic SIV and HIV infections is the functional and structural impairment of secondary lymphoid tissues due to a series of mechanisms including extensive virus trapping in follicular dendritic cells and virus replication in CD4+ follicular helper cells [11*,13*], disruption of the fibroblastic reticular network with increased collagen deposition, and reduced ability to generate new CD4+ T cells in response to homeostatic signals [14]. Of note, the structural impairment of lymph nodes can be recapitulated by the experimental depletion of CD4+ T cells in absence of SIV infection [15*], and is partially reserved by the administration of TNF antagonists during the acute phase of SIV infection [16*]. Additional advances on our understanding of CD4+ T cell dynamics during pathogenic lentiviral infections have been provided by experiments in which CD4+ T cells are depleted prior to SIV infection of macaques [17]. These studies have shown that CD4+ are essential to control SIV replication, and that their depletion is associated with increased virus replication, massive infection of macrophages, emergence of CD4+ independent envelope glycoproteins, and faster disease progression [17]. Several studies have shown that HIV disease progression is associated with a complex set of

mucosal immune abnormalities that result in the translocation of microbial products from the intestinal lumen to the portal and systemic circulations [18]. More recently, the concept of intestinal "disbyosis" (defined as an imbalance in the microbial species colonizing the gut) has been proposed as a factor contributing to AIDS pathogenesis [19]. Consistent with this idea is the recent finding that treatment with prebiotics/probiotics improves the immunological response to antiretroviral therapy in SIV-infected macaques [20**]. In ART treated HIV-infected humans persistent immune activation and incomplete immune reconstitution are associated with residual morbidity often referred to as "end-organ" disease. Similar observations have been made in SIV-infected macaques [21*], thus emphasizing the clinical relevance of this model. Importantly, the recent development of ART regimens that are highly effective in suppressing virus replication in SIV-infected macaques [22, 23, 24, 25*] will allow the in vivo testing of immune-based interventions aimed at reducing the residual mortality observed in ART-treated HIV-infected individuals.

Non-human primate models for HIV-1 vaccines and prevention

Non-human primate models have been at the forefront of efforts to identify the types of immune responses needed for protection against HIV-1 since the first report that animals infected with a *nef*-deleted strain of SIV were protected against subsequent wild-type SIV challenge [26]. *Nef*-deleted SIV, and other such live-attenuated strains, still afford the most reliable protection achieved in non-human primates, and although safety considerations preclude the use of live-attenuated HIV-1 in humans, identifying the correlates of protection by live-attenuated SIV may yield important insights for HIV-1 vaccine design. Recent studies have begun to reveal features of the immune responses elicited by live-attenuated SIV that may account for the robust protection provided by these strains. Perhaps the most fundamental difference from most other vaccine approaches is the ability of live-attenuated SIV to maintain ongoing antigenic stimulation as a result of persistent virus replication. A comprehensive analysis of protective immunity for six different live-attenuated strains differing in their degree of attenuation revealed that protection against intravenous challenge correlated with effector-differentiated $CD4^+$ and $CD8^+$ T cell frequencies in lymph nodes, but not in peripheral blood, and that the maintenance of these T cell responses was directly proportional to the amount of vaccine-strain replication [27**]. Based on these observations, it was proposed that live-attenuated SIV maintains sufficient activated effector memory T cells in lymph nodes to suppress, and in some cases to completely contain, early SIV replication at these sites. In another study, progressive increases in antibody titers capable of directing the killing of virus-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC) were associated with the time-dependent maturation of protection by live-attenuated SIV [28*]. While these correlative studies are limited in their ability to define mechanisms of protection, they nonetheless point to the importance of continuous antigenic stimulation in the maturation of protective immunity; perhaps by maintaining activated effector memory T cells in lymph nodes and/or by driving the affinity of maturation of envelope-specific antibodies.

Non-human primates have also been used extensively for proof-of-concept studies. Passive transfer experiments have demonstrated that certain HIV-specific neutralizing antibodies can provide complete protection against transmission of chimeric SHIVs expressing the HIV-1

envelope glycoprotein [29-30], indicating that a vaccine designed to elicit and to maintain such antibodies would protect against HIV-1. Unfortunately, such potent neutralizing antibodies have proven exceptionally difficult to elicit by vaccination. To circumvent the need to induce these antibodies by vaccination, adeno-associated virus (AAV) vectors are being explored for the direct delivery of immunoglobulin genes of pre-determined specificity. In an important proof-of-concept study, sustained neutralizing activity in serum for more than one year, and complete protection against an intravenous SIV challenge, was achieved after a single intramuscular inoculation of rhesus macaques with AAV vectors expressing Env-specific antibody-like immunoadhesins [31]. Numerous T cell-based vaccines have also been tested in non-human primates. In contrast to the complete protection that may be achieved with neutralizing antibodies, T cell-based vaccines do not prevent infection, but may result in the containment of virus replication, as measured by reductions in post-challenge viral loads, usually by about 1-2 logs, relative to unvaccinated control animals. A recent study in which *Mamu-B*08*$^+$ rhesus macaques (a model for elite control of HIV-1 by HLA-B*27$^+$ individuals [32]) were immunized against Mamu-B*08-restricted Nef and Vif epitopes achieved nearly complete suppression of chronic phase viral loads after SIV challenge [33*], thereby demonstrating both the potential of CD8$^+$ T cell responses to contain virus replication and the dependence of CD8$^+$ T cell protection on MHC class I genetics. Persistent vaccine vectors based on recombinant herpesviruses have also shown promise in recent studies. Immunization of rhesus macaques with rhesus cytomegalovirus (RhCMV) vectors expressing SIV antigens stimulated high frequencies of SIV-specific effector memory T cells, which were maintained indefinitely at potential sites of SIV replication, and resulted in the complete containment of SIV replication in approximately fifty percent of immunized animals after repeated low-dose intrarectal challenge [34]. Protection correlated with the magnitude of SIV-specific CD8$^+$ T cell responses, and was distinguished by a number of peculiar features, including the absence of Env-specific antibodies (despite the inclusion of an Env-expressing vector), the lack of anamnestic T cell responses after challenge, and the inability to partially control post-challenge viral loads in animals experiencing breakthrough SIV infection [34]. Another study in which rhesus macaques were immunized with non-persisting adenovirus and poxvirus vectors expressing SIV Env found that resistance to repeated, low-dose intrarectal SIV challenge correlated with Env-specific antibody titers [35**]. Although the majority of animals in this study ultimately became infected, Env-specific antibodies were associated with a reduced pre-exposure risk of SIV infection–analogous to the results of the RV144 trial, in which HIV-1 gp120-specific antibody titers were associated with a modest reduction in the rate of HIV-1 acquisition [36]. The picture that emerges from these vaccine studies is that there is probably more than one route to protection. Env-specific antibodies, if present at sufficient concentrations at sites of transmission, can prevent infection. Likewise, virus-specific T cells, if maintained in an activated effector memory state at sufficient frequencies, can contain virus replication below the threshold of detection at early sites of infection.

Non-human primate models for HIV-1 eradication and/or functional cure

In recent years, AIDS research has become more focused on studies of HIV eradication (defined as complete removal of the virus from the body) or functional cure (defined as a

persistently asymptomatic state with no detectable virus replication, normal immune function, and absence of virus transmission). This renewed focus has been prompted by continuous improvement in the portfolio of potent antiretroviral regimens and the description of the first case of long-term control of HIV in a patient who received stem cell transplantation from a CCR5delta32 homozygous donor [37]. These advances have prompted a number of investigators to consider therapeutic approaches aimed at achieving HIV eradication or functional cure by targeting the persistent reservoir of latently infected cells [22-25; 38]. Importantly, highly intensified ART regimens that suppress SIV replication in macaques have been developed [22-25], and the use of chimeric SHIV containing the HIV-1 Reverse Transcriptase (RT) gene (RT-SHIVs) have enabled NHP studies with drugs such as Efavirenz that are not effective against SIV [23]. It should be noted that this is a rapidly evolving field with novel information emerging almost daily in terms of ART regimens (efficacy, toxicity, pharmacokinetics), biology of the virus reservoirs, when virus replication is fully suppressed, role of non-CD4+ T cell reservoirs (i.e., macrophages, CNs, etc), and the efficacy of therapeutic approaches that selectively target these persistent virus reservoirs under ART.

While the NHP models for HIV eradication/functional cure are still relatively underdeveloped compared to those used in studies of HIV transmission, pathogenesis, and prevention, they hold much promise to advance this field due to several important specific experimental features (see Table 3). First, the use of NHP models allows the investigators to normalize the study for parameters that are virtually impossible to control in HIV-infected humans (i.e., identity, dose and route of inoculation of the virus; time of infection prior to initiation of ART; choice of the ART regimen; duration of ART, etc). Second, these studies allow for an extensive and detailed cellular and anatomical characterization of the virus reservoirs through aggressive tissue sampling (i.e., lymph nodes, mucosal tissues, CNS, etc), including elective necropsy. Third, NHP models allow pilot studies to be performed to test interventions at reducing viral reservoirs that would present unacceptable safety risks in humans (i.e., stem cell and gene therapies; combination immune-based approaches; interventions aimed at reactivating virus replication in latently infected cells) and in the context of additional experimental manipulations that would be virtually impossible to conduct in humans (structured treatment interruption; aggressive manipulations of the immune system such as CD4 or CD8+ lymphocyte depletions; etc). It should also be noted that the ongoing development of SIV/macaque models in which virus replication is fully suppressed by ART will ultimately create a research resource that could be used for both studies of HIV eradication/functional cure as well as study of the residual “end-organ” disease that is related to persistent immune activation and incomplete immune reconstitution.

Unfortunately, at this time, studies of ART-treated SIV/SHIV-infected macaques are problematic due to their high costs and long time to implementation, as each investigator has to build her/his own dedicated animal resource. It is possible that this situation discourages scientists from entering this field of research. A potential solution to this problem would be establishment of a centralized cohort of SIV/SHIV-infected macaques that are treated with ART and are available as a standardized research resource to investigators to test specific therapeutic concepts in a timely fashion. Such a cohort could also allow a more effective use

of the available financial resources due to economy of scale, and due to its standardized nature would allow for more accurate comparison between proposed interventions.

Conclusions

Studies of non-human primates infected with SIV or SHIV represent a mainstay in HIV/AIDS research, and continue to provide invaluable in vivo experimental data to inform and complement studies of the transmission, pathogenesis, prevention, and treatment of this devastating viral disease. It is anticipated that the continuous refinement of the existing models, particularly in the emerging area of virus “eradication” or “functional cure”, as well as the development of novel approaches, will further advance this field of research and ultimately translate into major benefits for the prevention and clinical management of HIV-infection.

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Key Points

1. The use of non-human primate models continues to be a mainstay in HIV-AIDS research and has led to a large number of significant advances in the field of HIV transmission, pathogenesis, prevention, and therapy
2. Recent studies of AIDS pathogenesis using the comparative models of pathogenic and non-pathogenic SIV infections support a model in which chronic immune activation, disruption of lymphoid tissue architecture, and preferential infection of CD4+ central memory cells are key contributors of HIV disease progression.
3. Advances in our understanding of the cell-mediated protection from HIV acquisition, early dissemination, and systemic replication have resulted from studies in which macaques have been immunized with persisting vectors such as rhesus CMV, live attenuated SIVs, and novel adenovirus-based immunogens.
4. The observation that passive transfer of HIV-specific neutralizing antibodies protects macaques from SHIV transmission landed much support to the theory that immunogens able to elicit such antibodies may represent effective AIDS vaccines.
5. The development of novel experimental models in which macaques are infected with SIV or SHIV and then treated with aggressive combination ART regimens that fully suppress virus replication might prove a formidable research tool for studies of HIV eradication/functional cure and residual morbidity under ART.

Table 1

Key Historical Results of AIDS Research in NHPs

1	Studies of the early events of virus transmission and dissemination.
2	Accurate immunological and virological analyses of the acute phase of infection.
3	Detailed characterization of the pathology in tissues.
4	Characterization of the in vivo role of specific viral proteins (i.e. delta Nef viruses etc)
5	Definition of the role of the host immune response in controlling virus replication by using “depletion” techniques.
6	Studies of pathogenesis using “invasive” techniques (i.e., repeated tissue sampling, cell labeling techniques, etc).
7	Definition of the mechanisms by which natural SIV hosts are resistant to AIDS despite high viremia.
8	Pre-clinical testing of candidate AIDS vaccines, microbicides, and ART strategies.

Table 2

Similarities between HIV & pathogenic SIV infection of macaques

1	Chronic progressive infection associated with opportunistic infections and CNS involvement (simian AIDS).
2	Presence of a minority of “benign” cases (LTNP, EC) associated with low viremia and specific MHC Class-I alleles.
3	Kinetics of viremia characterized by acute peak and post-peak decline.
4	Presence of vigorous but ultimately ineffective innate and adaptive immune responses to the virus.
5	Key pathogenic events include chronic immune activation, mucosal immune dysfunction, microbial translocation, and high levels of infection of central-memory CD4+ T cells.
6	Virus replication can be suppressed by ART with persisting reservoirs of latently infected cells.

Table 3

Opportunities provided by the NHP models in studies of HIV eradication

1	Identity, dose, and route of virus challenge known.
2	Control for various clinical parameters that are virtually impossible to control in humans (time of infection, duration of ART etc).
3	Comprehensive cellular and anatomic characterization of *both* active and persistent reservoirs (including elective necropsy).
4	Pilot trials of in vivo eradication conducted in a timely and controlled fashion; treatment interruption is possible.
5	Testing of “risky” interventions (i.e., cell depletion experiments, stem cell-based interventions etc).