Infection, Genetics and Evolution xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Non-human primates in HIV research: Achievements, limits and alternatives

Thalía Garcia-Tellez [a], Nicolas Huot [a,b], Mickaël J. Ploquin [a], Philippe Rascle [a], Beatrice Jacquelin [a], Michaela Müller-Trutwin [a,b,*]

[a] Institut Pasteur, Unité HIV, Inflammation and Persistence. 25–28 Rue du Doctor Roux,75015 Paris, France
[b] Vaccine Research Institute, Créteil, France

ARTICLE INFO

Article history:
Received 27 April 2016
Received in revised form 7 July 2016
Accepted 12 July 2016
Available online xxxx

Keywords:
HIV
SIV
AIDS
Non-human primates
Animal models

ABSTRACT

An ideal model for HIV-1 research is still unavailable. However, infection of non-human primates (NHP), such as macaques, with Simian Immunodeficiency Virus (SIV) recapitulates most virological, immunological and clinical hallmarks of HIV infection in humans. It has become the most suitable model to study the mechanisms of transmission and physiopathology of HIV/AIDS. On the other hand, natural hosts of SIV, such as African green monkeys and sooty mangabeys that when infected do not progress to AIDS, represent an excellent model to elucidate the mechanisms involved in the capacity of controlling inflammation and disease progression. The use of NHP-SIV models has indeed enriched our knowledge in the fields of: i) viral transmission and viral reservoirs, ii) early immune responses, iii) host cell-virus interactions in tissues, iv) AIDS pathogenesis, v) virulence factors, vi) prevention and vii) drug development. The possibility to control many variables during experimental SIV infection, together with the resemblance between SIV and HIV infections, make the NHP model the most appropriate, so far, for HIV/AIDS research. Nonetheless, some limitations in using these models have to be considered. Alternative models for HIV/AIDS research, such as humanized mice and recombinant forms of HIV-SIV viruses (SHIV) for NHP infection, have been developed. The improvement of SHIV viruses that mimic even better the natural history of HIV infection and of humanized mice that develop a greater variety of human immune cell lineages, is ongoing. None of these models is perfect, but they allow contributing to the progress in managing or preventing HIV infection.

1. Introduction

HIV/AIDS is still a major public health issue. According to the World Health Organization, HIV infection figures, even today, among the ten major leading causes of death and is the second cause of mortality in adolescents. Since the first report in 1981 and the identification of HIV as a causative agent in 1983 (Barré-Sinoussi et al., 2004), AIDS has claimed for >35 million of lives and only in 2015, 2.1 million of people became newly infected with HIV.

HIV infection is characterized by a slow and progressive loss of $CD4^+$ T cells that, in absence of treatment, generally leads to an immunosuppressive condition. Nowadays, it is admitted that chronic immune activation is the driving force of such immunodeficiency (Paiardini and Müller-Trutwin, 2013). Under successful combined antiretroviral therapy (cART), the virus is controlled up to undetectable level in blood, but a residual chronic inflammation persists and is associated with the morbidity and mortality observed in the antiretroviral-treated patients.

Despite of the great advances obtained in HIV/AIDS knowledge, there are still key problems to solve, in particular the lack of a vaccine and a cure and the absence of treatments for resolution of HIV-induced inflammation. Animal models for HIV have already contributed to answer major questions, but they also have several limitations. The "perfect animal model" for HIV-1 research is indeed still unavailable. However, infection of non-human primates (NHP), such as macaques, with Simian Immunodeficiency Virus (SIV) leads to a disease that is similar to AIDS induced by HIV in humans. So far, this is the most suitable model to study the mechanisms of transmission and physiopathology of the disease. Indeed, SIV infection in macaques fulfills numerous conditions generally requested to constitute a reliable animal model for a human disease:

1. The virus causing disease in the model should cause the same disease in humans;
2. The course of the disease in the animals should resemble that in humans;
3. The range of cells, tissues and organs involved should be similar in humans and in the animal;

* Corresponding author.
E-mail addresses: thalia.garcia-tellez@pasteur.fr (T. Garcia-Tellez), nicolas.huot@pasteur.fr (N. Huot), mickael.ploquin@pasteur.fr (M.J. Ploquin), philippe.rascle@pasteur.fr (P. Rascle), beatrice.jacquelin@pasteur.fr (B. Jacquelin), michaela.muller-trutwin@pasteur.fr (M. Müller-Trutwin).

http://dx.doi.org/10.1016/j.meegid.2016.07.012
1567-1348/

4. Immune responses to infection in the animal model should be similar to those in humans.

These conditions are not fulfilled by other animal models, such as FIV in cats or HIV-1 in humanized mice (see below). Here, we review characteristics of the SIV infection in NHP that have favored its use as a model for HIV/AIDS research and summarize some of the major past and recent advances in the field obtained thanks to the NHP models (Table 1). We will briefly evoke advances in other models, such as humanized mice, in research toward a HIV vaccine and cure. Finally, we will explain the limits of NHP models and discuss how these models could nonetheless help in the global effort to achieve the development of efficient preventive and cure approaches.

2. SIV models and their contributions to research on HIV prevention and treatment

Human AIDS is caused by two types of HIV (HIV-1 and HIV-2). These viruses are subdivided into groups (M, N, O, and P for HIV-1; A to I for HIV-2), subtypes, circulating recombinant forms (CRF) and unique recombinant forms (URF), HIV-1 group M subtype C being the most prevalent in the world (Peeters et al., 2013; Hemelaar, 2012).

Since the first cases of HIV infection, there has been interest in identifying the origin of the epidemic. The first insight came to light when a close relationship between HIV-2 and a virus that infects macaques was found (Chakrabarti et al., 1987). This virus was called SIVmac in analogy to HIV and according to the species from which it was isolated. Thereafter, another phylogenetic association was discovered between HIV-2 and SIVsmm, a virus that infects sooty mangabeys in West Africa (Hirsch et al., 1989). Subsequent studies confirmed that SIVmac and HIV-2 derived both from SIVsmm (Hirsch et al., 1989; Gao et al., 1999; Bailes et al., 2003; Chen et al., 1996).

The origin of HIV-1 was traced on non-human primates, as well. The human virus is closely related to SIVcpz, which infects West-Central Africa chimpanzees (*Pan troglodytes troglodytes*) (Gao et al., 1999; Bailes et al., 2003; Peeters et al., 1989; Simon et al., 1998; Corbet et al., 2000) and from which HIV-1 M and N derived (Simon et al., 1998; Corbet et al., 2000; Müller-Trutwin et al., 2000; Nerrienet et al., 2005; Keele et al., 2006; Peeters and Delaporte, 2012). On the other hand, the analysis of fecal samples from Cameroon gorillas revealed the existence of SIVgor (Van Heuverswyn et al., 2006; Plantier et al., 2009). The latter virus is related to HIV-1 O and P. Phylogenetic analyses indicate that chimpanzees constitute most likely the original reservoir and source of SIVgor as well as of HIV-1 O and P (Plantier et al., 2009; Takehisa et al., 2009; D'arc et al., 2015) (Fig. 1).

Table 1
Examples of major contributions of NHP models to HIV/AIDS research.

- Discovery of initial founder populations of infected cells (foci) (Haase (2010))
- CD8$^+$ T cell response: "too little, too late" to clear infection (Reynolds et al. (2005))
- Short window of opportunity to prevent infection (Sodora et al. (1998))
- CD8$^+$ T cells: impact on viral set-point (Nomura and Matano (2012); Letvin et al. (1999))
- Proof of concept that Nab can protect against infection (Barouch et al. (2015))
- Nef viral protein: necessary for high viral load *in vivo* (Kestler et al. (1991))
- Resting memory T cells: main target of the virus in lymphoid tissues (Mattapallil et al. (2005); Li et al. (2005))
- Rapid and dramatic depletion of CD4$^+$ T cells in gut (Veazey et al. (1998); Li et al. (2005))
- Trafficking of Treg, PDC, NK cells to the gut (Reeves et al. (2010a); Reeves et al. (2010b); Reeves et al. (2012))
- Loss of TCM associated with disease progression (Mattapallil et al. (2005); Picker et al. (2004))
- Events in acute infection determine disease progression (Saez-Cirion et al. (2014))
- TRIM5a alleles restrict viral replication *in vivo* (Reynolds et al. (2005))
- Analyses of the virome and microbiome in tissues (Barbian et al. (2015); Handley et al. (2016); Monaco et al. (2016); Palmer et al. (2016))
- *In vivo* imaging of SIV (Santangelo et al. (2015))

More than 40 NHP species have been found to carry SIV in the wild. Noteworthy, natural carriers of SIV are all African species. In contrast, Asian monkeys, such as macaques, are only infected in captivity.

The first report of AIDS in a NHP was provided by Letvin and cols in 1983 (Letvin et al., 1983), soon after the discovery of HIV. This syndrome was detected in captive macaques (*Macaca cyclopis* and *Macaca mulatta*) that died of lymphomas or opportunistic infections like *Pneumocystis carinii*. The revision of autopsy records and laboratory studies revealed that these animals suffered of anemia, neutropenia and monocytosis before decease. A lymphocyte ratio (CD4/CD8) reversion and a loss of T cell numbers and functionality were observed as well before death. The causes of death included necrotizing gingivitis, *Pneumocystis carinii* and cytomegalovirus infections, as well as three atypical cases of lymphoma.

Macaques infected by SIVmac became the most important animal model for HIV/AIDS research. The disease progression profile during SIV infections in macaques depends both on the macaque species and the SIVmac strain used (Fig. 2). The most frequently used animals are Indian and Chinese rhesus macaques as well as cynomolgus macaques infected by the SIVmac239 molecular clone or the SIVmac251 viral isolate. The most rapid disease progression is generally observed in Indian rhesus macaques infected with SIVmac239. This macaque model revealed the massive CD4$^+$ T cell depletion in the gut in the very early phase of infection (Veazey et al., 1998; Kewenig et al., 1999; Mattapallil et al., 2005). While it was already known that HIV replicates in the gut (Schneider et al., 1995), the macaque model helped to underscore the rapidity of the events in this tissue (within the first 24 h upon infection) and to what extent the degree of T lymphocyte loss in the gut is associated with disease progression. It was subsequently shown that resting memory CD4$^+$ T cells were the most frequently infected cells within the gastrointestinal (GI) tract (Brenchley et al., 2004; Li et al., 2005). These cells can live for decades and are now considered as a major reservoir for HIV-1 (Schmitz et al., 2012; Chomont et al., 2009).

Experimental SIV infections can be performed through the intravenous route. Several additional experimental protocols have been developed for infection through the rectal, vaginal or oral route in order to mimic the predominant routes of transmission encountered in humans, *i.e.* sexual or mother-to-child transmission by breast feeding (D'arc et al., 2015; Veazey et al., 1998; Kewenig et al., 1999; Mattapallil et al., 2005). To better resemble even more what is happening during infection and dissemination of the virus throughout the body in humans, protocols for repetitive low-dose challenges have been set up as well. These models contribute to evaluate vaccine candidates and already lead to the demonstration of two constructions that can confer strong control, *i.e.* SIVΔnef and rhesus cytomegalovirus (CMV)-based vectors. However, the degree of protection correlates inversely with the level of attenuation, the least-attenuated strain giving the greatest protection (Johnson and Desrosiers, 1998; Koff et al., 2006). Vaccine candidates based on CMV-vectors generate very strong and persistent T effector memory responses in half of the animals leading to a controlled infection and an elimination of viral reservoirs (Hansen et al., 2013). While it is at the moment unclear if such constructions can be used as a vaccine, the studies of these vaccine candidates have already and will continue to provide important clues about the correlates of protection against HIV (Daniel et al., 1992; Billingsley et al., 2015).

The macaque/SIVmac models also allow to examine the very first immunological events after viral exposure in relation to the transmission route or to study the selection mechanisms of transmitted/founder virus resulting from the genetic bottleneck that occurs during transmission (Table 1) (Sodora et al., 1998; Milush et al., 2004; Keele et al., 2009a; Tsai et al., 2014; Tully et al., 2016). It was shown for instance in the macaque model, that while in most cases the transmission is based on the selection and persistence of only one viral variant from the donor, the number of transmitted founder variants increases with the viral dose in the challenge (Fennessey and Keele, 2013; Ma et al., 2011; Keele and Estes, 2011; Gambhira et al., 2014).

Please cite this article as: Garcia-Tellez, T., et al., Non-human primates in HIV research: Achievements, limits and alternatives, Infection, Genetics and Evolution (2016), http://dx.doi.org/10.1016/j.meegid.2016.07.012