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Introduction

Beyond Specific Pathogen-Free: Biology and Effect of Common Viruses in Macaques

Nicholas W Lerche[1] and Joe H Simmons[2,*]

Macaque models have contributed to key advances in our basic knowledge of behavior, anatomy, and physiology as well as to our understanding of a wide variety of human diseases. This issue of *Comparative Medicine* focuses on several of the viral agents (members of *Retroviridae*, *Herpesviridae* and 2 small DNA viruses) that can infect both nonhuman primates and humans as well as confound research studies. Featured articles also address the challenges of developing colonies of macaques and other nonhuman primates that are truly specific pathogen-free for these and other adventitious infectious agents.

Abbreviations: SPF, specific pathogen free; SV40, *Simian virus 40*

As a group, nonhuman primates comprise our closest living animal relatives; in fact, humans and macaques shared a common ancestor as recently as 25 million years ago.[16] Because of their physical and physiologic similarity to humans, macaques have been used extensively in biomedical research for the past 500 y.[8] During this time, macaques have contributed to key progress in our basic understanding of behavior, anatomy, and physiology and the pathophysiology of a wide variety of human infectious diseases. In fact, macaques remain invaluable models in the study of AIDS, Parkinson disease, diabetes, obesity, and Alzheimer disease, for just a few examples.[21]

Adventitious infectious agents are well known to interfere with biomedical research by increasing morbidity, mortality, and variability, thus confounding research,[11,13,20,23] and macaques are susceptible to a variety of microbial agents that can infect humans as well.[1,3,4,9,22] To address these concerns as well as issues of colony health and animal welfare, a minimal definition of specific pathogen-free (SPF) was developed that includes animals that are free of B virus (*Cercopithecine herpesvirus 1*), SIV, simian type D retroviruses 1 through 5, simian T-lymphotropic virus, and *Mycobacterium tuberculosis*.[5,12,14] However, macaques are susceptible to numerous additional adventitious viruses, some of which cause life-long persistent or latent infections and potentially can confound research results. To increase awareness of these agents, the Association of Primate Veterinarians sponsored a seminar at the 2006 AALAS National Meeting titled *Beyond SPF: Biology and Impact of Common Viruses in Macaques*, at which several respected experts in the field of macaque diseases presented timely information on numerous macaque retroviruses, herpesviruses, and small DNA viruses (SV40 and parvoviruses). Many of the seminar participants and other authors have contributed articles to this issue of *Comparative Medicine.*

[1]*California National Primate Research Center, University of California, Davis, CA;* [2]*Charles River Laboratories, Wilmington, MA.*
[*]*Corresponding author. Email: joe.simmons@crl.com*

Retroviruses are a large and diverse group of enveloped, single-stranded, RNA viruses that are unique among viruses: they posses a complement of enzymes, including reverse transcriptase, that allows them to reverse-transcribe their RNA genomes into DNA and then insert that DNA into the genome of the host. Once the retrovirus is inserted into the host's chromosomes, it is called a 'DNA provirus.'[6] The integrated provirus enables retroviruses to persistently infect their host and avoid its immune system.[6,10] Table 1 lists some of the noteworthy macaque, human, and veterinary retroviruses. Currently 4 well-described retroviruses are known to infect laboratory macaques.

Herpesviruses are a highly varied group of enveloped, double-stranded, DNA viruses. All herpesviruses described to date have the capacity to undergo a period of latency after they infect their natural host. During latency, closed-circular viral DNA genomes can be found within cells, but only a subset of viral genes are expressed, and progeny virus is not present; however, the virus can reactivate from latency, replicate, and cause disease.[17] Viral latency can occur in a variety of differenct cell types depending upon the herpesvirus: for example, the *Simplexviruses* undergo latency in neurons of dorsal root ganglia, whereas *Lymphocryptoviruses* undergo latency in B lymphoctes.[17] The mechanisms of herpesvirus latency are not well understood, but the outcome of virus latency is persistent, lifelong infection. B virus is included on the minimal list of agents defining the SPF status of macaques primarily because this virus can cause fatal encephalomyelitis if it inadvertently infects humans;[4,18] however, reactivation during periods of immunosuppression or stress potentially can act as a confounding research variable as well. In addition to B virus, at least 5 other herpesviruses cause lifelong, latent, infections in macaques (Table 2).

In addition to retroviruses and herpesviruses, several other other viruses can infect macaques,[2] including simian polyomavirus (*Simian virus 40*; SV40) and *Simian parvovirus*. Although they belong to different families, SV40 and *Simian parvovirus* are both

Table 1. Common human and veterinary retroviruses

Family	Subfamily	Genus	Species
Retroviridae	*Orthoretrovirinae*	*Alpharetrovirus*	*Avian leukosis virus* *Rous sarcoma virus*
		Betaretrovirus	**Simian type D retrovirus (*Mason–Pfizer monkey virus*)** *Mouse mammary tumor virus*
		Gammaretrovirus	*Feline leukemia virus* *Gibbon ape leukemia virus* *Reticuloendotheliosis virus*
		Deltaretrovirus	Human T-lymphotropic virus **Simian T-lymphotropic virus** *Bovine leukemia virus*
		Epsilonretrovirus	*Walleye dermal sarcoma virus*
		Lentivirus	*Human immunodeficiency virus* ***Simian immunodeficiency virus*** *Feline immunodeficiency virus* *Visna/maedi virus*
	Spumaretrovirinae	*Spumavirus*	***Simian foamy virus*** *Feline foamy virus* *Bovine foamy virus* *Equine foamy virus*

Well-described macaque retroviruses are shown in bold.

Table 2. Common human and macaque herpesviruses

Family	Subfamily	Genus	Species
Herpesviridae	*Alphaherpesvirinae*	*Simplexvirus*	Herpes simplex viruses 1 and 2 (*Human herpesvirus 1* and *2*) **B virus (*Cercopithecine herpesvirus 1*)**
		Varicellovirus	Varicella–zoster virus (*Human herpesvirus 3*) **Simian varicella virus (*Cercopithecine herpesvirus 9*)**
	Betaherpesvirinae	*Cytomegalovirus*	Human cytomegalovirus (*Human cytomegalovirus 5*) **Rhesus cytomegalovirus (*Cercopithecine herpesvirus 8*)**
		Roseolovirus	*Human herpesvirus 6* and *7*
	Gammaherpesvirinae	*Lymphocryptovirus*	Epstein–Barr virus (*Human herpesvirus 4*) **Rhesus lymphocryptovirus (*Cercopithecine herpesvirus 15*)**
		Rhadinovirus	Kaposi sarcoma herpesvirus (*Human herpesvirus 8*) **Rhesus rhadinovirus (*Cercopithecine herpesvirus 17*)** **Retroperitoneal fibrosis herpesvirus**

Well-described macaque herpesviruses are shown in bold.

small, nonenveloped, DNA viruses; thus, they are quite stable and environmentally persistent. Both of these viruses have been associated with debilitiating disease in macaques that were immunosuppressed as a result of intercurrent retrovirus infection or as the result of a research protocol.[7,15,19]

Although 'super-clean' or 'super-SPF' macaques that are free of all or most of the earlier-described agents are not readily available to most researchers, colonies do exist within the NIH-funded National Primate Research Center Program. Because the availability of super-SPF macaques is limited, understanding the pathogensis of these adventitious viruses and how they might interfere with research can lead investigators to make proactive, informed, decisions about the potential effect on research, may help explain noted research variability, and can provide guidance in establishing humane study endpoints.

We hope that readers find the following articles informative, and we extend our thanks to the authors for their hard work and contributions.

References

1. **Adams SR, Muchmore E, Richardson JH.** 1995. Biosafety. In: Bennett TB, Abee CR, Henrickson R, editors. Nonhuman primates in biomedical research: Biology and management. San Diego: Academic Press. p 375–420.
2. **Bernacky BJ, Gibson SV, Keeling ME, Abee CR.** 2002. Nonhuman primates. In: Fox JG, Anderson LC, Loew FM, Quimby FW, editors. Laboratory animal medicine. New York: Academic Press. p 675–791.

3. **Calattini S, Betsem EBA, Froment A, Mauclere P, Tortevoye P, Schmitt C, Njouom R, Saib A, Gessain A.** 2007. Simian foamy virus transmission from apes to humans, rural Cameroon. Emerg Infect Dis **13:**1314–1320.
4. **Cohen JI, Davenport DS, Stewart JA, Deitchman S, Hilliard JK, Chapman LE.** 2002. Recommendations for prevention of and therapy for exposure to B virus (*cercopithecine herpesvirus* 1). Clin Infect Dis **35:**1191–1203.
5. **Desrosiers RC.** 1997. The value of specific pathogen-free rhesus monkey breeding colonies for aids research. AIDS Res Hum Retroviruses **13:**5–6.
6. **Goff SP.** 2001. *Retroviridae:* the retroviruses and their replication. In: Knipe DM, Howley PM, editors. Fields virology. Philadelphia: Lippincott Williams and Wilkins. p 1871–1939.
7. **Horvath CJ, Simon MA, Bergsagel DJ, Pauley DR, King NW, Garcea RL, Ringler DJ.** 1992. Simian virus 40-induced disease in rhesus monkeys with simian acquired immunodeficiency syndrome. Am J Pathol **140:**1431–1440.
8. **Johnson DO.** 1995. History. In: Bennett TB, Abee CR, and Henrickson R, editors. Nonhuman primates in biomedical research: biology and management. San Diego: Academic Press. p 1–14.
9. **Jones-Engel L, Engel GA, Schillaci MA, Rompis A, Putra A, Suaryana KG, Fuentes A, Beer B, Hicks S, White R, Wilson B, Allan JS.** 2005. Primate-to-human retroviral transmission in asia. Emerg Infect Dis **11:**1028–1035.
10. **Lerche NW.** 2005. Common viral infections of laboratory primates. In: Wolfe-Coote S, editor. The laboratory primate. London: Elsevier Academic Press. p 75–89.
11. **Lerche NW, Osborn KG.** 2003. Simian retrovirus infections: potential confounding variables in primate toxicology studies. Toxicol Pathol **31 Suppl:**103–110.
12. **Lerche NW, Yee JL, Jennings MB.** 1994. Establishing specific retrovirus-free breeding colonies of macaques: an approach to primary screening and surveillance. Lab Anim Sci **44:**217–221.
13. **Lipman NS, Perkins SE.** 2002. Factors that may influence animal research. In: Fox JG, Anderson LC, Loew FM, Quimby FW, editors. Laboratory animal medicine, 2nd ed. New York: Academic Press. p 1143–1184.
14. **Mansfield K.** 2005. Development of specific pathogen free nonhuman primate colonies. In: Wolfe-Coote S, editor. The laboratory primate. London: Elsevier Academic Press. p 229–239.
15. **O'Sullivan MG, Anderson DK, Lund JE, Brown WP, Green SW, Young NS, Brown KE.** 1996. Clinical and epidemiological features of simian parvovirus infection in cynomolgus macaques with severe anemia. Lab Anim Sci **46:**291–297.
16. **Rhesus Macaque Genome Sequencing and Analysis Consortium.** 2007. Evolutionary and biomedical insights from the rhesus macaque genome. Science **316:**222–234.
17. **Roizman B, Pellett PE.** 2001. The family *herpesviridae*: a brief introduction. In: Knipe DM, Howley PM, editors. Fields virology. Philadelphia: Lippincott Williams and Wilkins. p 2381–2397.
18. **Sabin AB, Wright AM.** 1934. Acute ascending myelitis following a monkey bite, with the isolation of a virus capable of reproducing the disease. J Exp Med **59:**115–136.
19. **Schroder C, Pfeiffer S, Wu G, Azimzadeh AM, Aber A, Pierson RN, 3rd, O'Sullivan MG.** 2006. Simian parvovirus infection in cynomolgus monkey heart transplant recipients causes death related to severe anemia. Transplantation **81:**1165–1170.
20. **Shek WR, Gaertner DJ.** 2002. Micorbiological quality control for laboratory rodents and lagomorphs. In: Fox JG, Anderson LC, Loew FM, Quimby FW editors. Laboratory animal medicine. New York: Academic Press. p 365–393.
21. **Sibal LR, Samson KJ.** 2001. Nonhuman primates: a critical role in current disease research. Ilar J **42:**74–84.
22. **Switzer WM, Bhullar V, Shanmugam V, Cong ME, Parekh B, Lerche NW, Yee JL, Ely JJ, Boneva R, Chapman LE, Folks TM, Heneine W**. 2004. Frequent simian foamy virus infection in persons occupationally exposed to nonhuman primates. J Virol **78:**2780–2789.
23. **van der Logt J.** 1993. Microbiological effects and quality control in laboratory rodents. Aging Clin Exp Res **5:**317–323.