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Simian Varicella Virus Pathogenesis

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Abstract

Because varicella zoster virus (VZV) is an exclusively human pathogen, the development of an animal model is necessary to study pathogenesis, latency, and reactivation. The pathological, virological, and immunological features of simian varicella virus (SVV) infection in nonhuman primates are similar to those of VZV infection in humans. Both natural infection of cynomolgus and African green monkeys as well as intrabronchial inoculation of rhesus macaques with SVV provide the most useful models to study viral and immunological aspects of latency and the host immune response. Experimental immunosuppression of monkeys latently infected with SVV results in zoster, thus providing a new model system to study how the loss of adaptive immunity modulates virus reactivation.

1 Introduction

During primary infection, varicella zoster virus (VZV) causes chickenpox in children, becomes latent in cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia along the entire neuraxis and reactivates decades later to produce zoster. With advancing age, a natural decline in cell-mediated immunity (CMI) to VZV causes reactivation of latent VZV resulting in zoster and postherpetic neuralgia as well as stroke from uni- or multifocal vasculopathy, myelitis, zoster paresis and even pain without rash (zoster sine herpete). All of these neurologic complications of zoster are increased in the rapidly expanding aging and immunocompromised population, especially in AIDS patients. Thus, a better understanding of VZV reactivation is essential.

VZV causes disease only in humans. Development of an experimental animal model that recapitulates the pathogenesis of VZV seen in humans has been a goal of several laboratories. Important criteria for any animal model of VZV latency include: (1) presence of virus nucleic acids in ganglia, but no, in non-ganglionic tissues; (2) presence of virus

exclusively in neurons; (3) limited transcription of virus genes; and (4) ability to reactivate the virus.

2 Animal Models of VZV Infection

There have been several attempts to generate an animal model of VZV infection (Table 1). Subcutaneous inoculation of VZV into the breast of a chimpanzee produced a mild rash near the site of infection with mild fever, but latency was not studied in this model (Cohen et al. 1996). Seroconversion in the absence of clinical signs was demonstrated by experimental inoculation of VZV into rabbits, mice, and rats (Myers et al. 1980,1985;Matsunaga et al. 1982;Wroblewska et al. 1982;Walz-Cicconi et al. 1986). Viral DNA was found in both ganglionic neurons and nonneuronal cells, as well as in non-ganglionic tissues 1 month after corneal inoculation of VZV in mice (Wroblewska et al. 1993) A papular exanthem without vesicles was seen in guinea pigs inoculated intramuscularly with VZV (Myers et al. 1991). VZV DNA was detected by PCR in ganglia of guinea pigs 80 days after subcutaneous inoculation (Lowry et al 1993). Although VZV RNA was detected in ganglia of guinea pigs by in situ hybridization at 5 weeks after ocular inoculation (Tenser and Hyman 1987), the absence of viral nucleic acids in non-ganglionic tissues has not been confirmed. Although no clinical signs developed, virus nucleic acids and proteins were detected in dissociated rat ganglionic neurons up to 9 months after experimental infection; however, although ganglia were cultured for 3–12 days, *in vitro* reactivation could not be excluded (Sadzot-Delvaux et al. 1990) Latent VZV infection was reported in rats inoculated via footpad and sacrificed 1 month later (Debrus et al. 1995;Kennedy et al. 2001), but the validity of the rat model is debatable since VZV DNA was not detected in ganglia 1–3 months after foot-pad-inoculation (Annunziato et al. 1998). Importantly, reactivation of latent VZV has not been demonstrated in any rodent species (Chen et al. 2003;Sadzot-Delvaux et al. 1990).

A SCID-humanized (SCID-hu) mouse model was developed in which human thymus and liver implants were introduced under the kidney capsule followed by subcutaneous introduction of skin implants from the same donor (Ku et al 2005). Direct inoculation of VZV into the skin implants results in virus infection as evidenced by the detection of virus proteins for 3 weeks after infection in CD4⁺ and CD8⁺ T cells of these mice (Moffat et al. 1995). These skin implants also become infected upon intravenous inoculation with VZV-infected human T cells (Ku et al. 2004). Because of the partially immunodeficient status of the mice, it is difficult to use this model to study the immune response of the host to VZV infection. Similar studies using human ganglionic implants have been used to demonstrate virus infection in SCID-hu mice (Zerboni et al. 2005).

3 Simian Varicella Virus

Simian varicella virus (SVV, *Cercopithecine herpesvirus 7*) causes chickenpox in nonhuman primates. SVV has been isolated during natural outbreaks in African green and Patas monkeys (Soike et al. 1984a). Clinical, pathological, immunological, and virological features of SVV infection in monkeys resemble those of human VZV infection (Wenner et al. 1977; Felsenfeld and Schmidt 1977, 1979; Padovan and Cantrell 1986; Myers and Connelly 1992; Dueland et al. 1992).

3.1 Clinical and Pathological Features

During primary SVV infection, infectious virus can be recovered at the peak of viremia from blood mononuclear cells (MNCs; Clarkson et al. 1967; Wolf et al. 1974; Soike et al. 1984a). SVV-induced rash is often hemorrhagic and disseminated (Soike 1992). Like disseminated VZV in immunosuppressed patients, lung and liver are the most severely affected organs (Roberts et al. 1984). Histological examination of skin and viscera reveals foci of

hemorrhagic necrosis, inflammation, and eosinophilic intranuclear inclusions (Clarkson et al. 1967; Wolf et al. 1974). Analysis of DNA extracted from multiple tissues 5 to 60 days post-infection (dpi) from intravenously inoculated monkeys demonstrated the time course and route of virus spread into sensory ganglia (Mahalingam et al. 2001). SVV DNA was detected in ganglia 6 dpi, before the appearance of rash. Intravenous inoculation produced more SVV DNA-positive ganglia (63%) than after intratracheal inoculation (13%), supporting the notion that like other organs, ganglia become infected by hematogenous spread of virus (Mahalingam et al. 2001).

3.2 Immunological Features

Like VZV infection in humans, recovery from SVV infection in monkeys correlates with both humoral and cellular immune responses. The antibody response to SVV has been investigated in several nonhuman primate species, including Patas, African green monkeys, and rhesus macaques. In Patas monkeys, SVV-specific IgM antibodies were detected using a high sensitivity double sandwich ELISA 5–8 days after subcutaneous inoculation, with a peak titer 10–15 dpi, a decline in titer 17–22 dpi, and eventual disappearance within 2 months (Iltis et al. 1984). IgG antibodies appeared 10–12 dpi, reaching a plateau 17–19 dpi and remained stable for at least 2 months (Iltis et al. 1984; Achilli et al. 1984). Viremia preceded detectable IgM antibody by 2 days, and the appearance of IgG coincided with the end of viremia (Iltis et al. 1984). Neutralizing antibodies develop in St. Kitts vervet monkeys 10–14 dpi and increase in titer until 21 dpi thereafter remaining at stable levels for at least 2 months (Gray et al. 1998). The antibody response to SVV is directed against several polypeptides, some of which are glycosylated (Gray et al. 1995). The exact identity of these polypeptides has not been elucidated, and the kinetics of the neutralizing antibody response remains to be determined. The immune response to SVV plays a critical role in protection against disease, as evidenced by resistance to reinfection and viremia after SVV challenge in animals that recover from SVV infection (Gray et al. 1995; Messaoudi et al. 2009).

3.3 Virological Features

SVV and VZV have similar size, structure, and genomic organization, with an estimated 70–75% DNA homology (Gray et al. 1992, 2001; Pumphrey and Gray 1992). The two viruses encode polypeptides that are antigenically related. Immunization of monkeys with VZV protects monkeys from SVV infection (Felsenfeld and Schmidt 1979). In serum neutralization and complement fixation tests, SVV-specific antibodies cross-react with human VZV (Felsenfeld and Schmidt 1979; Soike et al. 1987; Fletcher and Gray 1992).

3.4 Features of Latency and Reactivation

Like VZV infection in humans, SVV becomes latent in ganglionic neurons at multiple levels of the neuraxis (Mahalingam et al. 2002; Kennedy et al. 2004) after primary infection. The pattern of SVV transcription in latently infected monkey ganglia is similar to that of VZV transcription in latently infected human ganglia, with minor differences such as the presence of sense and antisense SVV ORF 61 transcripts in monkey ganglia but their absence in human ganglia during latency (Messaoudi et al. 2009).

Latent SVV reactivates in naturally infected monkeys exposed to social and environmental stress (Soike et al. 1984b). Epizootic SVV infections have been associated with transportation of monkeys or introduction of new monkeys into an existing colony (Clarkson et al. 1967; McCarthy et al. 1968; Soike 1992). Between 1966 and 1989, several SVV outbreaks were observed in primate centers in the USA and UK, most of which were attributed to reactivation of latent SVV (Gray 2004). Unlike VZV reactivation in humans, zoster in primates often appears as a whole-body rash lasting less than 1 week, albeit obscured by fur. Although neither VZV nor SVV can be isolated from blood in otherwise

healthy immunocompetent seropositive humans or primates, SVV has been isolated from skin vesicles after reactivation (Soike et al. 1984a) and also during primary infection and reactivation in the same monkey (Gray and Gusick 1996).

4 Experimental SVV Infection

Three models of experimental SVV infection have been generated. The first is intratracheal inoculation of SVV into African green and cynomolgus monkeys, which results in persisting viremia for months to years (White et al. 2002a, b). The second involves simulated natural infection, which produces latency and which has been used to demonstrate experimental reactivation (Mahalingam et al. 2002). The last model is intrabronchial inoculation of SVV into rhesus macaques, which provides a novel model to analyze viral and immunological mechanisms of varicella latency (Messaoudi et al. 2009). The latter two models are the best-suited for future studies involving SVV latency and reactivation. Each one of the three models is discussed in detail below.

4.1 Model 1: Persistent Viremia

Experimental intratracheal inoculation of 10^4 pfu of SVV in African green and Cynomolgus monkeys produces vesicular skin rash 7–10 dpi. Viremia is detectable 3 dpi, peaks 5 dpi, and disappears by 11 dpi, indicating hematogenous spread of virus. At the peak of rash, SVV produces hepatitis and pneumonia. Resolution of rash correlates with the detection of virus-specific antibody by 12 dpi (Wenner et al. 1977; Iltis et al. 1982; Soike et al. 1984a; Dueland et al. 1992; Gray et al. 1998; Gray 2003). During acute infection, virus antigens and nucleic acids have been found in multiple organs, including lung, liver, spleen, adrenal gland, kidney, lymph node, bone marrow, and in ganglia at all levels of the neuraxis (Wenner et al. 1977; Roberts et al. 1984; Padovan and Cantrell 1986; Dueland et al. 1992; Gray et al. 2002). In African green monkeys, serum-neutralizing antibodies are commonly detected by 14 dpi and reach peak levels 21 dpi (Soike et al. 1984b; Gray et al. 1995). Levels of neutralizing antibodies remain stable for at least 4 months after SVV infection.

SVV DNA continues to persist for months to years in several tissues, including ganglia, liver, and blood MNCs in monkeys inoculated intratracheally with SVV (White et al. 2002a). Multiple regions of SVV DNA are found in blood MNCs from SVV-infected monkeys 7 dpi and 10 months post-infection (mpi) (White et al. 2002b). This is best explained by infection of MNCs that traffic through infected tissue in which SVV DNA persists. Virus could not be recovered 14 mpi, from monkey kidney cells that had been co-cultivated with blood MNCs, even after multiple sub-cultivations (White et al. 2002b). At 14 mpi, SVV DNA was found in CD4+ and CD8+ cells, but not in CD14+ or CD20+ cells (White et al. 2002b). Earlier studies in VZV demonstrated that during chickenpox, virus DNA and antigens are present in human T and B cells, monocytes, and macrophages, but infectious VZV was recovered from macrophages and T lymphocytes (Arbeit et al. 1982; Koropchak et al. 1989; Soong et al. 2000). Multiple attempts to infect MNCs *in vitro* with VZV suggest that these cells are only semi-permissive to VZV (Arbeit et al. 1982; Gilden et al. 1987; Koropchak et al. 1989; Soong et al. 2000; Zerboni et al. 2000). In this model, Grinfeld and Kennedy (2007) showed that SVV DNA was present in both neuronal as well as nonneuronal satellite cells 9–10 mpi and only in neurons 2 years post-infection. Transcripts specific for immediate-early, early, and late SVV genes are present in lung, liver, and ganglia (White et al. 2002a). Ou et al. (2007) reported the detection of transcripts specific for SVV ORFs 21, 29, and 63, as well as both sense and antisense RNA with respect to SVV ORF 61, in ganglia of vervet monkeys that were inoculated intratracheally multiple times with SVV.

4.2 Model 2: Latency

Intrabronchial inoculation of rhesus macaques with SVV produced rash, viremia, and both humoral and cell-mediated immune responses to SVV in all monkeys (Messaoudi et al. 2009). SVV-specific IgG were first detected 10–12 days after intrabronchial inoculation, and the titers peaked 7 days later. Analysis of the kinetics and magnitude of the T cell response was based on measuring changes in T cell proliferation, IFN γ /TNF α secretion, and granzyme B (a marker for T cells with cytotoxic potential) production in peripheral blood as well as bronchial alveolar lavage (BAL) and revealed a proliferative burst of T cells in both peripheral blood and BAL first detected 7 dpi that peaked 14 dpi. Similarly, CD4 $^{+}$ T cells that produce IFN γ /TNF α in response to SVV viral lysate stimulation *ex vivo* were first detected 7 dpi as determined by intracellular cytokine staining. The frequency of SVV-specific CD4 $^{+}$ T cells peaked 14 dpi, after which it decreased and remained stable up to 73 dpi. Prevalence of granzyme B-expressing T cells among effector memory CD4 $^{+}$ and CD8 $^{+}$ T cells increased 7 dpi and remained high until 28 dpi before returning to pre-infection frequencies, indicating that SVV infection elicits a T cell response with cytotoxic potential.

Months after resolution of varicella, SVV DNA was detected only in ganglia but not in lung or liver. Furthermore, like VZV, SVV displayed limited transcriptional activity. We detected transcripts corresponding to SVV ORFs 21, 62, 63, and 66 but not 40 (a late gene) in latently infected ganglia. However, unlike in VZV latency, we detected sense as well as the much more abundant antisense transcripts specific 10 SVV ORF 61 (Messaoudi et al. 2009) consistent with the observations of Ou et al. (2007) in vervet monkeys inoculated intratracheally multiple times with SVV. Detection of sense or antisense SVV ORF 61 transcript monkey ganglia warrants more detailed analysis of latently infected human ganglia for VZV ORF 61 transcripts. Finally, like VZV latency in human ganglia, SVV ORF 63 protein was detected exclusively in the cytoplasm of monkey ganglia latently infected with SVV (Fig. 1). Overall, intratracheal inoculation of SVV into rhesus macaques results in the establishment of latency (Messaoudi et al. 2009).

4.3 Model 3: Latency and Reactivation

We developed a model of latent SVV infection in both African green and cynomolgus monkeys by exposing seronegative monkeys to others that had been inoculated intratracheally with SVV (Mahalingam et al. 2002). Naturally exposed monkeys develop varicella 10–12 days after exposure. SVV infection was confirmed by DNA PCR analysis of skin scrapings during varicella. SVV DNA was occasionally present in blood MNCs, and SVV DNA was detected 6–8 weeks after resolution of rash in multiple ganglia along the entire neuraxis, but not in lung or liver, indicating the establishment of latency. Latent SVV was localized exclusively in ganglionic neurons (Kennedy et al. 2004). While natural infection resulted in latency in sensory ganglia, seroconversion was random, and viremia was not found in most animals.

Although spontaneous reactivation of SVV has been observed in naturally infected monkeys in primate centers around the world (Treuting et al. 1998; Gray 2004), experimental reactivation has not been attempted until recently. We observed subclinical reactivation of latent SVV in an irradiated rhesus macaque that resulted in disseminated varicella in another monkey housed in the same colony (Kolappaswamy et al. 2007). In addition, papulovesicular dermatitis caused by reactivation of latent SVV in immunosuppressed rhesus macaques has been reported (Schoeb et al. 2008).

Based on the spontaneous development of zoster in AIDS patients as well as organ transplant recipients and cancer patients treated with X-irradiation, immunosuppressive drugs, and steroids (Dolin et al. 1978), we used the natural infection paradigm to establish

latent SVV infection in four cynomolgus monkeys, and 3 months after varicella, the monkeys were irradiated and treated with tacrolimus and prednisone. Of the four latently infected monkeys that were immunosuppressed and subjected to the stress of transportation and isolation, one developed zoster and three developed subclinical reactivation in the absence of rash. A non-immunosuppressed latently infected monkey subjected to the same stress showed features of subclinical reactivation. SVV reactivation was confirmed not only by the occurrence of zoster in one monkey, but also by the presence of SVV RNA specific to late capsid proteins (ORFs 40 and 9) in ganglia, the presence of SVV DNA in non-ganglionic tissue, and the detection of SVV antigens in skin, ganglia (including axons), and lung (Mahalingam et al. 2007). Recently, we found that SVV reactivates in monkeys treated with tacrolimus with or without exposure to irradiation (unpublished observations).

5 Conclusions

Intrabronchial inoculation of rhesus macaques and simulated natural infection of African green and cynomolgus monkeys are best-suited to study SVV latency and reactivation. Although zoster in humans is directly related to a decline in CMI to VZV, virus-specific T cells are not seen in ganglia harboring latent VZV or SVV (Verjans et al. 2007; Messaoudi et al. unpublished observations). Experimental reactivation of SVV in primates can be used to examine the role of T cells in the maintenance of latent infection in ganglia. While VZV downregulates MHC I surface expression and its retention in golgi bodies (Cohen 1998; Abendroth et al. 2001; Einfeld et al. 2007), varicella latency may also be regulated by an innate immune response involving cytokines or chemokines.

SVV infection in the monkeys will, for the first time, allow analysis of the cascade of cellular, immune, and viral factors involved in reactivation. This is important since reactivation in elderly and immunocompromised individuals can produce serious, often chronic, and sometimes fatal neurological disease. Furthermore, an SVV reactivation model will be useful in testing preventive vaccines, antiviral drugs, SVV strain differences, age factors, as well as other variables.

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Abbreviations

CMI	Cell-mediated immunity
MNCs	Mononuclear cells
ORF	Open reading frame
SVV	Simian varicella virus
VZV	Varicella zoster virus

References

- Abendroth A, Lin I, Slobedman B, et al. Varicella-zoster virus retains major histocompatibility complex class I proteins in the Golgi compartment of infected cells. *J Virol.* 2001; 75:4878–4888. [PubMed: 11312359]
- Achilli G, Sarasini A, Gerna G, et al. Antibody response of patas monkeys to experimental infection with Delta herpesvirus. *Eur J Clin Microbiol.* 1984; 3:158–159. [PubMed: 6723641]

- Annunziato P, LaRussa P, Lee P, et al. Evidence of latent varicella-zoster virus in rat dorsal root ganglia. *J Infect Dis*. 1998; 178(Suppl 1):S48–S51. [PubMed: 9852973]
- Arbeit RD, Zaia JA, Valerio MA, et al. Infection of human peripheral blood mononuclear cells by varicella-zoster virus. *Intervirology*. 1982; 18:56–65. [PubMed: 6288616]
- Chen JJ, Gershon AA, Li ZS, et al. Latent and lytic infection of isolated guinea pig enteric ganglia by varicella zoster virus. *J Med Virol*. 2003; 70(Suppl 1):S71–S78. [PubMed: 12627492]
- Clarkson MJ, Thorpe E, McCarthy K. A virus disease of captive vervet monkeys (*Cercopithecus aethiops*) caused by a new herpesvirus. *Arch Gesamte Virusforsch*. 1967; 22:219–234. [PubMed: 4301195]
- Cohen JI. Infection of cells with varicella-zoster virus down-regulates surface expression of class I major histocompatibility complex antigens. *J Infect Dis*. 1998; 177:1390–1393. [PubMed: 9593031]
- Cohen JI, Moskal T, Shapiro M, et al. Varicella in chimpanzees. *J Med Virol*. 1996; 50:289–292. [PubMed: 8950684]
- Debrus S, Sadzot-Delvaux C, Nikkels AF, et al. Varicella-zoster virus gene 63 encodes an immediate-early protein that is abundantly expressed during latency. *J Virol*. 1995; 69:3240–3245. [PubMed: 7707559]
- Dolin R, Reichman RC, Mazur MH, et al. NIH conference. Herpes zoster-varicella infections in immunosuppressed patients. *Ann Intern Med*. 1978; 89:375–388. [PubMed: 210697]
- Dueland AN, Martin JR, Devlin ME, et al. Acute simian varicella infection: clinical laboratory, pathologic, and virologic features. *Lab Invest*. 1992; 66:762–773. [PubMed: 1602744]
- Eisfeld AJ, Yee MB, Erazo A, et al. Downregulation of class I major histocompatibility complex surface expression by varicella-zoster virus involves open reading frame 66 protein kinase-dependent and -independent mechanisms. *J Virol*. 2007; 81:9034–9049. [PubMed: 17567702]
- Felsenfeld AD, Schmidt NJ. Antigenic relationships among several simian varicella-like viruses and varicella-zoster virus. *Infect Immun*. 1977; 15:807–812. [PubMed: 192676]
- Felsenfeld AD, Schmidt NJ. Varicella-zoster virus immunizes patas monkeys against simian varicella-like disease. *J Gen Virol*. 1979; 42:171–178. [PubMed: 215708]
- Fletcher TM, Gray WL. Simian varicella virus: characterization of virion and infected cell polypeptides and the antigenic cross-reactivity with varicella-zoster virus. *J Gen Virol*. 1992; 73:1209–1215. [PubMed: 1316940]
- Gilden DH, Hayward AR, Krupp J, et al. Varicella-zoster virus infection of human mononuclear cells. *Virus Res*. 1987; 7:117–129. [PubMed: 3035815]
- Gray WL. Pathogenesis of simian varicella virus. *J Med Virol*. 2003; 70(Suppl 1):S4–S8. [PubMed: 12627479]
- Gray WL. Simian varicella: a model for human varicella-zoster virus infections. *Rev Med Virol*. 2004; 14:363–381. [PubMed: 15386593]
- Gray WL, Gusick NJ. Viral isolates derived from simian varicella epizootics are genetically related but are distinct from other primate herpesviruses. *Virology*. 1996; 224:161–166. [PubMed: 8862410]
- Gray WL, Pumphrey CY, Ruyechan WT, et al. The simian varicella virus and varicella zoster virus genomes are similar in size and structure. *Virology*. 1992; 186:562–572. [PubMed: 1310185]
- Gray WL, Gusick NJ, Fletcher TM, et al. Simian varicella virus antibody response in experimental infection of African green monkeys. *J Med Primatol*. 1995; 24:246–251. [PubMed: 8750501]
- Gray WL, Williams RJ, Chang R, et al. Experimental simian varicella virus infection of St. Kitts vervet monkeys. *J Med Primatol*. 1998; 27:177–183. [PubMed: 9879858]
- Gray WL, Starnes B, White MW, et al. The DNA sequence of the simian varicella virus genome. *Virology*. 2001; 284:123–130. [PubMed: 11352673]
- Gray WL, Mullis L, Soike KF. Viral gene expression during acute simian varicella virus infection. *J Gen Virol*. 2002; 83:841–846. [PubMed: 11907334]
- Grinfeld E, Kennedy PG. The pattern of viral persistence in monkeys intra-tracheally infected with simian varicella virus. *Virus Genes*. 2007; 35:289–292. [PubMed: 17253123]
- Iltis JP, Arrons MC, Castellano GA, et al. Simian varicella virus (delta herpesvirus) infection of patas monkeys leading to pneumonia and encephalitis. *Proc Soc Exp Biol Med*. 1982; 169:266–279. [PubMed: 6278510]

- Itlis JP, Achilli G, Madden DL, et al. Serologic study by enzyme-linked immunosorbent assay of the IgM antibody response in the patas monkey following experimental simian varicella virus infection. *Diagn Immunol*. 1984; 2:137–142. [PubMed: 6094088]
- Kennedy PG, Grinfeld E, Bontems S, et al. Varicella-zoster virus gene expression in latently infected rat dorsal root ganglia. *Virology*. 2001; 289:218–223. [PubMed: 11689044]
- Kennedy PGE, Grinfeld E, Traina-Dorge V, et al. Neuronal localization of simian varicella virus DNA in ganglia of naturally infected African green monkeys. *Virus Genes*. 2004; 28:273–276. [PubMed: 15266108]
- Kolappaswamy K, Mahalingam R, Traina-Dorge V, et al. Disseminated simian varicella virus infection in an irradiated rhesus macaque (*Macaca mulatta*). *J Virol*. 2007; 81:411–415. [PubMed: 17079326]
- Koropchak CM, Solem SM, Diaz PS, et al. Investigation of varicella-zoster virus infection of lymphocytes by in situ hybridization. *J Virol*. 1989; 63:2392–2395. [PubMed: 2539528]
- Ku CC, Zerboni L, Ito H, et al. Varicella-zoster virus transfer to skin by T cells and modulation of viral replication by epidermal cell interferon- α . *J Exp Med*. 2004; 200:917–925. [PubMed: 15452178]
- Ku CC, Besser J, Abendroth A, et al. Varicella-zoster virus pathogenesis and immunobiology: new concepts emerging from investigations with the SCIDhu mouse model. *J Virol*. 2005; 79:2651–2658. [PubMed: 15708984]
- Lowry PW, Sabella C, Koropchak CM, et al. Investigation of the pathogenesis of varicella-zoster virus infection in guinea pigs by using polymerase chain reaction. *J Infect Dis*. 1993; 167:78–93. [PubMed: 8380293]
- Mahalingam R, Wellish M, Cohrs R, et al. Expression of protein encoded by varicella-zoster virus open reading frame 63 in latently infected human ganglionic neurons. *Proc Natl Acad Sci USA*. 1996; 93:2122–2124. [PubMed: 8700895]
- Mahalingam R, Wellish M, Soike K. Simian varicella virus infects ganglia before rash in experimentally infected monkeys. *Virology*. 2001; 279:339–342. [PubMed: 11145914]
- Mahalingam R, Traina-Dorge V, Wellish M, et al. Naturally acquired simian varicella virus infection in African green monkeys. *J Virol*. 2002; 76:8548–8550. [PubMed: 12163574]
- Matsunaga Y, Yamanishi K, Takahashi M. Experimental infection and immune response of guinea pigs with varicella-zoster virus. *Infect Immun*. 1982; 37:407–412. [PubMed: 6288560]
- McCarthy K, Thorpe E, Laursen AC, et al. Exanthematous disease in patas monkeys caused by a herpes virus. *Lancet*. 1968; 2:856–857. [PubMed: 4175746]
- Messaoudi I, Barron A, Wellish M, et al. Simian varicella virus infection of rhesus macaques recapitulates essential features of varicella zoster virus infection in human. *PLoS Pathog*. 2009; 5(11):1–14.
- Moffat JF, Stein MD, Kaneshima H, et al. Tropism of varicella-zoster virus for human CD4+ and CD8+ T lymphocytes and epidermal cells in SCID-hu mice. *J Virol*. 1995; 69:5236–5242. [PubMed: 7636965]
- Myers MG, Connelly BL. Animal models of varicella. *J Infect Dis*. 1992; 166(Suppl 1):S48–S50. [PubMed: 1320650]
- Myers MG, Duer HL, Hausler CK. Experimental infection of guinea pigs with varicella-zoster virus. *J Infect Dis*. 1980; 142:414–420. [PubMed: 6255038]
- Myers MG, Stanberry LR, Edmond BJ. Varicella-zoster virus infection of strain 2 guinea pigs. *J Infect Dis*. 1985; 151:106–113. [PubMed: 2981274]
- Myers MG, Connelly BL, Stanberry LR. Varicella in hairless guinea pigs. *J Infect Dis*. 1991; 163:746–751. [PubMed: 1849161]
- Ou Y, Davis KA, Traina-Dorge V, et al. Simian varicella virus expresses a latency-associated transcript that is antisense to open reading frame 61 (ICP0) mRNA in neural ganglia of latently infected monkeys. *J Virol*. 2007; 81:8149–8156. [PubMed: 17507490]
- Pavan-Langston D, Dunkel EC. Ocular varicella-zoster virus infection in the guinea pig: a new *in vivo* model. *Arch Ophthalmol*. 1989; 107:1058–1072.
- Padovan D, Cantrell CA. Varicella-like herpesvirus infections of nonhuman primates. *Lab Anim Sci*. 1986; 36:7–13. [PubMed: 3007865]

- Pumphrey CY, Gray WL. The genomes of simian varicella virus and varicella zoster virus are colinear. *Virus Res.* 1992; 26:255–266. [PubMed: 1337232]
- Roberts ED, Baskin GB, Soike K, et al. Pathologic changes of experimental simian varicella (Delta herpesvirus) infection in African green monkeys (*Cercopithecus aethiops*). *Am J Vet Res.* 1984; 45:523–530. [PubMed: 6711981]
- Sadzot-Delvaux C, Merville-Louis MP, Delree P, et al. An *in vivo* model of varicella-zoster virus latent infection of dorsal root ganglia. *J Neurosci Res.* 1990; 26:83–89. [PubMed: 2359148]
- Sato H, Persnicak L, Cohen JI. Use of a rodent model to show that varicella-zoster virus ORF61 is dispensable for establishment of latency. *J Med Virol.* 2003; 70(Suppl 1):S79–S81. [PubMed: 12627493]
- Schoeb TR, Eberle R, Black DH, et al. Diagnostic exercise: papulovesicular dermatitis in rhesus macaques (*Macaca mulatta*). *Vet Pathol.* 2008; 45:592–594. [PubMed: 18587109]
- Soike KF. Simian varicella virus infection in African and Asian monkeys. The potential for development of antivirals for animal diseases. *Ann NY Acad Sci.* 1992; 653:323–333. [PubMed: 1320844]
- Soike KF, Baskin G, Cantrell C, et al. Investigation of antiviral activity of I-beta-D-arabinofuranosylthymine (ara-T) and I-beta-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil (BV-ara-U) in monkeys infected with simian varicella virus. *Antiviral Res.* 1984a; 4:245–257. [PubMed: 6097178]
- Soike KF, Rangan SR, Gerone PJ. Viral disease models in primates. *Adv Vet Sci Comp Med.* 1984b; 28:151–199. [PubMed: 6098169]
- Soike KF, Keller PM, Ellis RW. Immunization of monkeys with varicella-zoster virus glycoprotein antigens and their response to challenge with simian varicella virus. *J Med Virol.* 1987; 22:307–313. [PubMed: 3040898]
- Soong W, Schultz JC, Patera AC, et al. Infection of human T lymphocytes with varicella-zoster virus: an analysis with viral mutants and clinical isolates. *J Virol.* 2000; 74:1864–1870. [PubMed: 10644359]
- Tenser RB, Hyman RW. Latent herpesvirus infections of neurons in guinea pigs and humans. *Yale J Biol Med.* 1987; 60:159–167. [PubMed: 3495074]
- Treuting PM, Johnson-Delaney C, Birkebak TA. Diagnostic exercise: vesicular epidermal rash, mucosal ulcerations, and hepatic necrosis in a *Cynomolgus* monkey (*Macaca fascicularis*). *Lab Anim Set.* 1998; 48:384–386.
- Verjans GM, Hintzen RQ, van Dun JM, et al. Selective retention of herpes simplex virus-specific T cells in latently infected human trigeminal ganglia. *Proc Natl Acad Sci USA.* 2007; 104:3496–3501. [PubMed: 17360672]
- Walz-Cicconi MA, Rose RM, Dammin GJ, et al. Inoculation of guinea pigs with varicella-zoster virus via the respiratory route. *Arch Virol.* 1986; 88:265–277. [PubMed: 3010908]
- Wenner HA, Abel D, Barrick S, et al. Clinical and pathogenetic studies of Medical Lake macaque virus infections in *Cynomolgus* monkeys (simian varicella). *J Infect Dis.* 1977; 135:611–622. [PubMed: 192806]
- White TM, Mahalingam R, Traina-Dorge V, et al. Simian varicella virus DNA is present and transcribed months after experimental infection of adult African green monkeys. *J Neurovirol.* 2002a; 8:191–203. [PubMed: 12053274]
- White TM, Mahalingam R, Traina-Dorge V, et al. Persistence of simian varicella virus DNA in CD4(+) and CD8(+) blood mononuclear cells for years after intratracheal inoculation of African green monkeys. *Virology.* 2002b; 303:192–198. [PubMed: 12482671]
- Wolf RH, Smetana HF, Allen WP, et al. Pathology and clinical history of Delta herpesvirus infection in patas monkeys. *Lab Anim Sci.* 1974; 24:218–221. [PubMed: 4360748]
- Wroblewska Z, Devlin M, Reilly K, et al. The production of varicella zoster virus antiserum in laboratory animals. *Arch Virol.* 1982; 74:233–238. [PubMed: 6299237]
- Wroblewska Z, Valyi-Nagy T, Otte J, et al. A mouse model for varicella-zoster virus latency. *Microb Pathog.* 1993; 15:141–151. [PubMed: 8255207]
- Zerboni L, Sommer M, Ware CF, et al. Varicella-zoster virus infection of a human CD4-positive T-cell line. *Virology.* 2000; 270:278–285. [PubMed: 10792986]

Zerboni K, Ku CC, Jones CD, et al. Varicella-zoster virus infection of human dorsal root ganglia in vivo. *Proc Natl Acad Sci USA*. 2005; 102:6490–6495. [PubMed: 15851670]

Fig. 1.

Detection of VZV and SVV ORF 63 proteins in the cytoplasm of neurons in ganglia of a human latently infected with VZV and a rhesus macaque latently infected with SVV. Paraformal-dehyde-fixed, paraffin-embedded sections of thoracic ganglia from a VZV seropositive 46-year-old man (**a**) (Mahalingam et al. 1996) and from a rhesus macaque latently infected with SVV (**b**) (Messaoudi et al. 2009) were analyzed by immunohistochemistry using rabbit anti-VZV ORF 63. Both VZV and SVV ORF 63 proteins are located exclusively in the cytoplasm of neurons in the respective ganglia. The *arrows* indicate the location of ORF 63 protein in the neuronal cytoplasm. Figure 1a reprinted with permission of National Academy of Sciences, USA (Mahalingam et al. (1996); Copyright 1996 National Academy of Sciences. USA); and Fig. 2b PLoS pathogens (Messaoudi et al. 2009)

Table 1

Results of attempts to produce VZV-induced disease in animals

Species	Route of inoculation	Sero-conversion	Rash (dpi)	Viremia	Time of sacrifice	Detection of SVV nucleic acids in tissue				References	
						ganglionic					
						hyb ¹	PCR	neuronal	Non-neuronal		
chimpanzee	subcutaneous	+	10	+	nd	nd	nd	nd	nd	Cohen et al. 1996	
guinea pig	intranasal/corneal	+	4	nd	nd	nd	nd	nd	nd	Matsumaga et al. 1982	
guinea pig	intramuscular	+	9–25	+	23 d	+2	nd	nd	nd	+	Myers et al. 1985
guinea pig	intratracheal	+	–	nd	60 d	nd	nd	nd	nd	nd	Walz-Cicconi et al. 1986
guinea pig	ocular	nd ³	–	nd	21 d	nd	nd	nd	nd	nd	Pavan–Langstan and Dunkel 1989
guinea pig	intramuscular	+	4–7	+	nd	na ⁴	na	na	na	na	Myers et al. 1991
guinea pig	subcutaneous	nd	+ ⁵	+	80 d	+2	+	nd	nd	nd	Lowry et al. 1993
guinea pig	corneal	nd	nr ⁶	nd	35 d	+ ⁷	+	–	–	nd	Tenser and Hyman 1987
rat	subcutaneous	+	none	nd	9 m	+ ⁷	nd	+	nd	nd	Sadzot-Delvaux et al. 1990
rat	subcutaneous	nd	nr	nd	30 d	nd	nd	+	+	nd	Debrus et al. 1995
rat	subcutaneous	nd	nr	nd	18 m	+ ⁷	+	+	+	nd	Kennedy et al. 2001
rat	subcutaneous	+	none	–	1–3 m	+ ⁷	+	+	+	nd	Annunziato et al. 1998
rat	intramuscular	nd	nr	nd	1 m		+	nd	nd	nd	Sato et al. 2003
mouse	subcutaneous	+	nr	nd	4–9 d	nd	nd	nd	nd	nd	Wroblewska et al. 1982
mouse	corneal	+	none	nd	33 d	+ ⁷	+	+	+	nd	Wroblowska el al. 1993
SCID-hu-mouse	skin implants	na	na	nd	nd	nd	nd	nd	nd	nd	Moffat et al. 1995
SCID-hu-mouse	ganglia implants	na	na	na	14 d	nd	+	+	–	nd	Zerboni et al. 2005

¹ hybridization

² dot blot

³ not done

⁴ not applicable

⁵ dpi not reported

6 not reported
7 insitu

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