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Animal models of highly pathogenic RNA viral infections: Hemorrhagic fever viruses

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Abstract

A diverse group of highly pathogenic RNA viruses cause a severe multisystemic illness in humans commonly referred to as viral hemorrhagic fever (VHF). Although they can vary widely in clinical presentation, all VHFs share certain features that include intense fever, malaise, bleeding and shock. Effective antiviral therapies for most of the VHFs are lacking. Complicating development of intervention strategies is the relative infrequency and unpredictability of VHF outbreaks making human clinical trials extremely challenging or unfeasible. Therefore, animal models that can recapitulate human disease are essential to the development of effective antivirals and vaccines. In general, a good animal model of VHF will demonstrate systemic dispersion of the virus through infection of mononuclear phagocytes and dendritic cells, which induces the release of inflammatory mediators that increase vascular permeability and facilitate coagulation. The culmination of this process leads to significant loss of plasma volume and terminal hypovolemic shock. Although it is clear that nonhuman primate models are the most faithful to human disease, the more accessible and less costly rodent models, including those based on infection with related surrogate viruses, can reproduce certain components of VHF and can serve as suitable preclinical models for initial development of effective countermeasures. Such models are sufficient for testing of drugs that directly block viral replication, but may be inadequate for evaluating therapies that depend for their success on the activation or inhibition of host responses.

Keywords: Animal model; RNA virus; Viral hemorrhagic fever; Flavivirus; Bunyavirus; Arenavirus; Lassa fever; Junin virus; Argentine hemorrhagic fever; Filovirus; Ebola virus; Marburg virus; Yellow fever; Dengue hemorrhagic fever; Dengue virus; Rift Valley fever; Crimean-Congo hemorrhagic fever; Hantavirus; Hantaviral pulmonary syndrome; Hemorrhagic fever with renal syndrome

1. Introduction

As the name implies, viral hemorrhagic fevers (VHFs) are maladies characterized by fever and bleeding, but they vary in their clinical features depending on the etiological agent involved. Hemorrhage can be a prominent feature in the clinical picture of certain VHFs, but explicit bleeding is generally only seen in the most severe cases and is usually associated with marked thrombocytopenia (Chen and Cosgriff, 2000). It is actually the impairment of the vascular system (plasma volume loss) which often has catastrophic consequences that lead to death by hypovolemic shock (Bray, 2005).

Viruses that cause hemorrhagic fever (HF) belong to one of four taxonomic families, *Arenaviridae*, *Bunyaviridae*, *Filoviridae* or *Flaviviridae*. The increased potential for intentional release and the lack of FDA-approved therapies to treat these frequently deadly infections has become a major concern for public health officials worldwide (Borio et al., 2002). With the exception of dengue virus, all VHF agents are maintained in nature in wild or domesticated mammals. The flaviviral HFs, Rift Valley fever and Crimean-Congo HF are arthropod-borne diseases, whereas arenaviral and hantaviral HFs are primarily acquired through exposure to aerosolized rodent excreta. The natural mode of transmission and the reservoir for the filoviruses, Ebola and Marburg, have not been identified.

The geographic ranges of VHF agents are restricted to the distribution of their vectors and reservoir hosts. In reservoir species, infections are generally mild or inapparent. In humans, who are accidental hosts, viral subversion of the type I interferon response (Basler, 2005) and overzealous proinflammatory

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mediator production are considered to be major contributing factors to the failure to control infection and the severe disease that ensues (Bray, 2005). Although our understanding of pathogenetic mechanisms specific to the various types of VHFs is incomplete, recent studies with several HF viruses have provided valuable insights into the virus–host interaction. Macrophages and dendritic cells (DCs), which normally play a crucial role in controlling viral infections, are readily infected and likely serve as vehicles for systemic dissemination (Baize et al., 2004; Bosio et al., 2003; Feldmann et al., 1996; Geisbert et al., 2003b; Ho et al., 2001; Kyle et al., 2007; Mahanty et al., 2003b). Sustained high-level activation mediated by the release of proinflammatory factors, some of which recruit additional mononuclear phagocytes to the site of infection, combined with the high viremia produce an acute incapacitating disease state.

Ideally, the spectrum of disease in an animal model should resemble that of the human condition. Reservoir hosts are generally not suitable animal models since they do not respond to their respective viral infections in a manner analogous to the human response. A good VHF animal model should be based on the primary infection of macrophages, monocytes, and DCs, with subsequent unchecked viral dissemination to other organs and tissues. Most types of VHF are associated with significant liver disease, which likely originates either from circulatory failure or through the spread of infection through the bloodstream to Kuppfer cells, with subsequent spill-over into parenchymal cells; with the exception of yellow fever, it is rarely the cause of death (Child et al., 1967; Geisbert et al., 2003b; Geisbert and Jahrling, 2004; Monath, 2008; Peters et al., 1988; Terrell et al., 1973; Walker et al., 1982b). Hepatic dysfunction that resembles the clinical picture seen in humans is often represented in the more faithful animal models.

In broad terms, there are five types of animal models in use for antiviral drug evaluation. First and foremost are nonhuman primates, wherein the infecting VHF agents produce severe disease without any preliminary adaptation. However, because of logistical aspects and the cost-prohibitive nature of conducting primate studies, rodent models are most commonly used. These can be divided into those in which a HF virus produces lethal infection without any prior adaptation and those that require serial passage of virus to elicit severe disease. The fourth model system is based on infection with phylogenetically related, but less pathogenic "surrogate" viruses that produce disease in rodents resembling that caused by the respective HF virus in humans. These systems make up the vast majority of the models that are covered in this review. A fifth category consists of those rodent models that use newborn or suckling animals and/or unconventional routes of viral inoculation (e.g. intracranial) to produce lethal infection, and are generally considered to be poor models that do not accurately portray human disease. The utility of such models is limited to assessing the effects of antivirals in the context of a living system, and, therefore, only those for which no other options are available have been included in this review.

The main objective of this compilation is to provide the research community with a guide to the principal animal models available for the study of highly pathogenic RNA viral infections that can lead to VHF. Animal models for highly pathogenic RNA viruses that cause severe encephalitis are discussed in an accompanying review (Holbrook and Gowen, 2008). For the majority of the VHFs, there are no effective antiviral therapies, or there are only limited efficacy data in humans. Ribavirin may be effective for some VHFs in the event of an emergency, but there are currently no FDA-approved therapies for the treatment of these life-threatening infections. The sporadic nature of VHF outbreaks in locations often far removed from adequate medical facilities makes it particularly difficult to evaluate countermeasures against most of these viruses. As such, researchers must rely heavily on the use of animal model systems to advance therapeutic interventions to a stage where they can actually be used to treat VHFs. Herein we review the current status of animal models that can be used to gain further insights into VHF disease pathogenesis, the development of vaccines, and evaluation of potential antiviral therapies for the treatment of these frequently fatal diseases.

2. Arenaviral HF animal models

2.1. Lassa fever (LF)

Of VHFs of arenaviral origin, LF has had the greatest impact on public health, with an estimated 100,000–300,000 people infected annually and death tolls of 5000 people per year in endemic regions of Western Africa (CDC, 2004; Khan et al., 2008). Consequently, modeling of LF has been a priority as reflected by the number of currently available model systems (Table 1). Compared to other VHFs, LF is more insidious in nature and the most frequently observed pathological findings including hepatocellular, adrenal and splenic necrosis do not readily explain the shock characteristic of fatal cases (Walker et al., 1982b). The principal LF model in nonhuman primates is based on infection of rhesus macaques (Table 1). This model has proven to be predictive in the evaluation of ribavirin (Jahrling et al., 1980), which has been shown to be effective in treating LF in humans (McCormick et al., 1986a).

Other primate models, including infection of rhesus macaques with the WE strain of lymphocytic choriomeningitis virus (Lukashevich et al., 2003) and the recently described marmoset LASV model (Carrion et al., 2007) have been introduced but are yet to be widely accepted as models that accurately portray authentic LF disease. Notably, all three nonhuman primate models of LF do reproduce diffuse pantropic infection with characteristic hepatocellular necrosis similar to that documented in human disease (McCormick et al., 1986b; Walker et al., 1982b). Like the macaque model, LASV infection of marmosets appears to correspond well with the human condition (Carrion et al., 2007). Because of the much smaller size of the common captive marmoset (320–450 g), the tremendous expense of conducting nonhuman primate LF studies may be considerably reduced, especially if breeding colonies can be established in-house. Although some reactivity with antibodies directed at human antigens has been documented (Carrion et al., 2007), it remains to be seen whether the frequent cross-reactivity

Table 1
Principal animal models for the study of arenaviral HFs

Virus	Disease modeled	Animal model	Selected references
Lassa	Lassa fever	Rhesus macaque	Stephen and Jahrling (1979), Jahrling et al. (1980), Walker et al. (1982a), Callis et al. (1982), Fisher-Hoch et al. (1987)
Lymphocytic choriomeningitis	Lassa fever	Rhesus macaque	Lukashevich et al. (2003), Djavani et al. (2007)
Lassa	Lassa fever	Marmoset	Carrion et al. (2007)
Lassa	Lassa fever	Guinea pig	Jahrling et al. (1982), Jahrling (1983)
Pichinde	Lassa fever	Guinea pig[a]	Jahrling et al. (1981), Lucia et al. (1989), Aronson et al. (1994), Zhang et al. (1999), Zhang et al. (2001)
Pichinde	Lassa fever	Hamster	Buchmeier and Rawls (1977), Smee et al. (1993), Gowen et al. (2005), Gowen et al. (2006d), Gowen et al. (2007a)
Pirital	Lassa fever	Hamster	Xiao et al. (2001b), Sbrana et al. (2006a)
Junin	Argentine hemorrhagic fever	Rhesus macaque	McKee et al. (1987), Green et al. (1987)
Junin	Argentine hemorrhagic fever	Marmoset	Weissenbacher et al. (1979), Gonzalez et al. (1983), Weissenbacher et al. (1986)
Junin	Argentine hemorrhagic fever	Guinea pig	Oubina et al. (1984), Kenyon et al. (1985), Kenyon et al. (1986), Kenyon et al. (1988), Kenyon et al. (1990)
Guanarito	Venezuelan hemorrhagic fever	Guinea pig	Hall et al. (1996)
Machupo	Bolivian hemorrhagic fever	Rhesus macaque	Terrell et al. (1973), Kastello et al. (1976), Gonder and Eddy (1986)
Machupo	Bolivian hemorrhagic fever	African green monkey	Wagner et al. (1977), McLeod et al. (1978)

[a] Virus adapted to produce lethal disease.

of human reagents that facilitates research using macaques will also be the case with marmosets.

The guinea pig has also been used to model LF (Table 1), with inbred strain 13 animals being highly susceptible to wild-type LASV infection and the outbred Hartley strain being much less susceptible to lethal disease (<30% mortality). The strain 13 model is the preferred system as it is uniformly lethal and reproduces many aspects of LF seen in humans and experimentally infected rhesus macaques (Jahrling et al., 1982). The Hartley model may be useful for investigating host factors that distinguish nonfatal from fatal infection. It is not, however, suitable for antiviral or vaccine studies because of the low mortality rate of untreated infection and the consequent requirement for large numbers of animals to permit adequate statistical analysis. Models based on infection with high-passage strains of the less pathogenic Pichinde arenavirus (PICV) have also been established in both the less accessible strain 13 and the readily available Hartley guinea pig (Table 1). These have been fairly well characterized, demonstrating systemic multiorgan infection that principally targets macrophages (Aronson et al., 1994; Jahrling et al., 1981).

Models of LF have also been developed in hamsters through infection with nonadapted PICV or Pirital virus (PIRV), with the former being routinely used for antiviral studies (Table 1). Due to the great expense of conducting antiviral evaluations under BSL-4 containment and the fact that there are only a limited number of institutions that can perform such studies, the availability of surrogate virus models requiring less stringent biocontainment (PICV, BSL-2; PIRV, BSL-3) is ideal for early stage preclinical development of candidate therapies that directly target steps in viral replication. Critical aspects of the treatment regimen for a given species can be worked out in these more accessible systems prior to transition to infection with authentic LASV in high-containment laboratories. With the exception of ribavirin, which was tested in the PICV guinea pig (Lucia et al., 1989) and hamster (Smee et al., 1993) models after efficacy had already been documented in humans (McCormick et al., 1986a), it remains to be seen whether successful therapy in rodents will accurately predict efficacy in nonhuman primates.

2.2. South American HFs (SAHFs)

Several New World arenaviruses, including Junin (JUNV), Machupo (MACV), Guanarito (GTOV), and Sabia (SABV) are also known to cause VHF, endemic in various regions of South America. Disease models with several of the SAHF-causing arenaviruses have been developed (Table 1). In contrast to LASV, infection with certain SAHF viruses can result either in HF or in central nervous system disease. Argentine HF (causative agent, JUNV) has been the most studied with established rhesus macaque, marmoset and guinea pig models. In the rhesus macaque (Green et al., 1987; McKee et al., 1987) and guinea pig (Kenyon et al., 1988), viscerotropism or neurotropism appears to be virus strain-dependent, as has also been reported in human cases. Thus, it may be possible to model both forms of disease for evaluating potential therapeutics. The marmoset model has been used to evaluate ribavirin (Weissenbacher et al., 1986). Significant protection was seen following treatment of infected marmosets with ribavirin, which is consistent with the reported efficacy against JUNV infection in humans (Enria et al., 2008). Bolivian (causative agent, MACV) and Venezuelan (causative agent, GTOV) HF have been modeled in several species of monkeys and guinea pigs, respectively, and appear to be adequate models of human disease (Table 1). Although LF and the SAHFs differ in certain aspects of their pathogenesis (Geisbert and Jahrling, 2004), much of what has been learned from LF models in the context of antiviral studies may be applicable to the SAHFs, and vice-versa. Caution must be used, however, since ST-294, a small molecule inhibitor of New World arenaviruses that likely blocks virus entry into host cells was

found to be inactive against LASV (Bolken et al., 2006), possibly due to differences in host cell receptor usage (Cao et al., 1998; Radoshitzky et al., 2007).

3. Bunyaviral HF animal models

3.1. Rift Valley fever (RVF)

Rift Valley fever virus (RVFV), genus *Phlebovirus*, is the etiological agent of RVF, a mosquito-borne illness that is primarily endemic in sub-Saharan Africa. Infection normally results in a febrile illness that resolves without complications; however, in severe cases, HF with marked hepatitis are the most prominent features, with encephalitis occurring less frequently (Morrill and McClain, 1996). Of all types of VHF, RVF has the largest number of different animal models to study the disease (Table 2). Models based on infection with RVFV consist of mouse (Kende et al., 1985), hamster (Niklasson et al., 1984), rat (Anderson et al., 1987), and rhesus macaque (Peters et al., 1986). The virus differs in its lethality in these models, but in most produces a high-level viremia with characteristic hepatocellular necrosis being a salient feature. There is also an age-dependent gerbil RVFV infection model that produces encephalitis in young animals (Anderson et al., 1988). Somewhat of a limiting factor in RVFV research is that "enhanced" BSL-3 (also known as "BSL-3+" or "Agricultural BSL-3") facilities required for handling pathogenic strains of RVFV are not readily accessible to most researchers. As with the arenaviral HF viruses, several surrogate virus models are available.

Punta Toro virus (PTV) is a closely related phlebovirus that produces a fatal hepatic disease in mice similar to that caused by RVFV in humans and livestock (Table 2). Initially described in weanling mice (Pifat and Smith, 1987), it was recently found that mature mice (≥8-week-old) also develop lethal illness after PTV challenge (Gowen et al., 2006b). The latter model provides flexibility to conduct extended prophylaxis and vaccine studies that could not be previously done in the less desirable weanling mouse model. There is also a hamster PTV infection model for which the disease more closely resembles severe RVF in humans including evidence of intestinal hemorrhaging (Anderson et al., 1990). Hamsters are highly susceptible to infection requiring ∼1000-fold less infectious virus per gram of body weight compared to mice. A recent report suggests that the evaluation of immunotherapies that elicit protective immunity in hamsters, compared to mice, will likely be more predictive of the human response (Gowen et al., 2006c). Safe to work with in BSL-2 containment facilities, PTV small animal infection models have been used to evaluate a number of potential antiviral agents (Gowen et al., 2006a; Gowen et al., 2007a,b; Sidwell et al., 1988a,b; Sidwell et al., 1992; Smee et al., 1991). Another available RVF model is the hamster Gabek Forest phlebovirus (GFV) infection model (Table 2). This alternative system also produces a fulminant hepatic disease and pathogenesis comparable to that produced by PTV in hamsters and RVFV in humans (Fisher et al., 2003). BSL-3 facilities are required for working with this model, which may be useful to study phleboviral pathogenesis, but it has yet to be used to test antiviral drugs.

3.2. Crimean-Congo HF (CCHF)

Another important bunyaviral HF restricted to the Eastern hemisphere results from infection with CCHF virus (CCHFV), genus *Nairovirus* (Ergonul, 2008). CCHF is a tick-borne disease that is found in locations where its tick vectors thrive, ranging from Western China to Southern Europe and down to South Africa. In Turkey, where the disease is endemic, more than 400 cases were documented in 2006, up from ∼250 in 2004 and 2005 (Vatansever et al., 2007). Through the first 8 months of

Table 2
Principal animal models for the study of bunyaviral HFs

Virus	Genus	Disease modeled	Animal model	Selected references
Rift Valley	*Phlebovirus*	Rift Valley fever	Rhesus macaque	Peters et al. (1986), Peters et al. (1988), Morrill et al. (1989)
Rift Valley	*Phlebovirus*	Rift Valley fever	Rat	Anderson et al. (1987), Bird et al. (2007)
Rift Valley	*Phlebovirus*	Rift Valley fever	Hamster	Niklasson et al. (1984), Peters et al. (1986)
Rift Valley	*Phlebovirus*	Rift Valley fever	Gerbil	Anderson et al. (1988)
Rift Valley	*Phlebovirus*	Rift Valley fever	Mouse	Kende et al. (1985), Peters et al. (1986)
Punta Toro	*Phlebovirus*	Rift Valley fever	Hamster	Anderson et al. (1990), Fisher et al. (2003), Gowen et al. (2006c), Perrone et al. (2007), Gowen et al. (2007a)
Gabek Forest	*Phlebovirus*	Rift Valley fever	Hamster	Fisher et al. (2003)
Punta Toro	*Phlebovirus*	Rift Valley fever	Mouse	Pifat and Smith (1987), Sidwell et al. (1994), Gowen et al. (2006a), Gowen et al. (2006b), Gowen et al. (2007a)
Crimean-Congo hemorrhagic fever	*Nairovirus*	Crimean-Congo hemorrhagic fever	Mouse (newborn)	Tignor and Hanham (1993)
Hantaan	*Hantavirus*	Hemorrhagic fever with renal syndrome	Mouse (suckling)	Kim and McKee (1985), McKee et al. (1985), Huggins et al. (1986)
Puumala	*Hantavirus*	Hemorrhagic fever with renal syndrome	Cynomolgus macaque	Groen et al. (1995), Klingstrom et al. (2002)
Andes	*Hantavirus*	Hantavirus pulmonary syndrome	Hamster	Hooper et al. (2001), Campen et al. (2006), Wahl-Jensen et al. (2007)
Maporal	*Hantavirus*	Hantavirus pulmonary syndrome	Hamster	Milazzo et al. (2002)

2007, the total number of cases has exceeded 500, presumably because of higher temperatures in this region (O. Ergonul, personal communication). Despite this emerging problem and the potential biothreat associated with CCHFV infection, research on the disease has been hindered by the lack of animal models (Table 2). Unlike most HF agents, CCHFV has not been found to cause disease in commonly used species of nonhuman primates.

A CCHFV infant mouse infection model has been reported wherein high infectious viral titers were demonstrated in the blood and liver, with Kuppfer cells staining positive for viral antigen (Tignor and Hanham, 1993). Although there is evidence of systemic viral dissemination and infection of macrophages in infant mice, consistent with the paradigm of VHF, virus could not be isolated from the spleen, where large numbers of mononuclear phagocytes reside, after the second day of infection. In this single report describing CCHFV infection of infant mice, significantly decreased mortality and extended survival was evident in infected animals treated with ribavirin. In accordance, oral ribavirin therapy has shown some success in the treatment of patients diagnosed with CCHF (Ergonul et al., 2004; Fisher-Hoch et al., 1995). Thus, despite the inherent flaws of the CCHFV newborn mouse infection model, it may have some predictive value in identifying antiviral drugs that directly inhibit viral replication. To date, no further studies have been conducted using this model, in spite of the clear need for antiviral drugs to treat CCHF, a disease with mortality rates reported in the range of 10–50% (CDC, 2005). Because the immune response in humans is believed to play a key role in the development of VHF diseases, the underdeveloped immune component of newborn mice is less than ideal when attempting to model the disease. As such, efforts to develop a better animal model have begun at USAMRIID (C. Whitehouse, personal communication).

3.3. Hantaviral HFs

The *Hantavirus* genus of the *Bunyaviridae* family also includes several viruses that can cause severe disease in humans (Schmaljohn and Hjelle, 1997). Old World hantaviruses cause a form of HF that is characterized by clinically significant kidney disease as well as other more variable disease signs and symptoms (Lee and van der Groen, 1989). The term HF with renal syndrome (HFRS) is commonly used when referring to such diseases caused primarily by Hantaan (HTNV), Seoul (SEOV), Dobrava (DOBV), and Puumala (PUUV) viruses. HFRS is predominantly a Eurasian disease that varies in severity, with HTNV and DOBV infections being the most lethal and PUUV infections having the lowest mortality rates (Schmaljohn and Hjelle, 1997). Unfortunately, there is a lack of robust animal models to study HFRS (Table 2), with the only ones reported being a suckling mouse HTNV infection model (Kim and McKee, 1985) and a non-lethal macaque PUUV infection model (Groen et al., 1995). The relevance of these models is questionable, as they do not faithfully reproduce human disease.

Hantavirus pulmonary syndrome (HPS), is a disease confined to the Americas caused by infection with one of several New World hantaviruses, of which Andes and Sin Nombre viruses are most frequently associated with fatal outcomes (Wahl-Jensen et al., 2007). Although hemorrhage is not seen in HPS, respiratory failure resulting from vascular leakage is a prominent feature of the disease (Peters et al., 1999), and therefore, a brief description of animal models of HPS warrant inclusion in this review. Currently there are only two available models that reproduce many aspects of human disease (Table 2). Both are based in hamsters, with Andes virus (ANDV) producing a uniformly fatal infection (Hooper et al., 2001), while Maporal virus (MPRLV) infection is reportedly less lethal (Milazzo et al., 2002). In addition to the uniform lethality of the ANDV model that makes it amenable to drug and vaccine efficacy studies, many similarities to human HPS exist including short time to death following the onset of symptoms, labored breathing, pleural effusion, pathology of the liver and spleen, and hypotension (Campen et al., 2006; Hooper et al., 2001; Wahl-Jensen et al., 2007). The MPRLV model also has many of the aforementioned features, including the less than uniform mortality seen in human cases of HPS (CDC, 2007). It is important to recognize that immune-mediated pathogenesis likely plays an important role in human disease. Thus, direct antiviral efficacy demonstrated in hamster HPS models may not translate into successful treatment of the human condition. In this issue focusing on the treatment of highly pathogenic RNA viral infections, Jonsson et al. (2008) describe the HPS models in greater detail.

4. Filoviral HF animal models

4.1. Ebola HF (EHF)

Filoviruses cause the deadliest of the VHFs with case fatality rates that can approach 90% during disease outbreaks (Bausch et al., 2008; Mahanty and Bray, 2004). EBOV infection in nonhuman primates has been intensively investigated. Disease produced in infected macaques has served as the prototypical model for the study of VHF pathogenesis. Infectious challenge of macaques with EBOV sets off the cardinal VHF disease features characterized by infection of macrophages and dendritic cells, rapid systemic viral dissemination, immunosuppression through antagonism of the type I interferon response and induction of lymphocyte apoptosis, infection of hepatocytes and other parenchymal cells, coagulation defects, and increased vascular permeability resulting in terminal shock (Baize et al., 1999; Bowen et al., 1978; Feldmann et al., 1996; Fisher-Hoch et al., 1985; Geisbert et al., 2003b,c,d). Bowen et al. (1978) first reported uniformly fatal EBOV infection in rhesus macaques and African green monkeys (Table 3). Cynomolgus macaques are equally susceptible to infection. With the exception of uniform lethality and the speed in which it kills, experimental infection of macaques by injection, aerosol inhalation, or placement in the eye or mouth, results in a severe disease that closely resembles human EHF (Bray and Geisbert, 2005). A number of studies exploring various countermeasures against EBOV infection in monkeys have been conducted using both rhesus and cynomolgus macaques (Feldmann et al., 2007; Geisbert et al., 2003a; Geisbert et al., 2002; Jahrling et al., 1996a; Jones et al., 2005; Oswald et al., 2007; Sullivan et al., 2000; Warfield et al., 2006).

Table 3
Principal animal models for the study of filoviral HFs

Virus	Disease modeled	Animal model	Selected references
Ebola	Ebola hemorrhagic fever	Rhesus macaque	Bowen et al. (1978), Fisher-Hoch et al. (1983), Fisher-Hoch et al. (1985), Geisbert et al. (2003a), Warfield et al. (2006), Feldmann et al. (2007), Oswald et al. (2007), Bukreyev et al. (2007)
Ebola	Ebola hemorrhagic fever	Cynomolgus macaque	Jahrling et al. (1996a,b), Sullivan et al. (2000), Geisbert et al. (2002), Geisbert et al. (2003b,d), Reed et al. (2004), Jones et al. (2005)
Ebola	Ebola hemorrhagic fever	Guinea pig[a]	Lupton et al. (1980), Xu et al. (1998), Connolly et al. (1999), Parren et al. (2002)
Ebola	Ebola hemorrhagic fever	Mouse[a]	Bray et al. (1998), Huggins et al. (1999), Gibb et al. (2001), Mahanty et al. (2003a), Warfield et al. (2003), Enterlein et al. (2006)
Marburg	Marburg hemorrhagic fever	Rhesus macaque	Daddario-DiCaprio et al. (2006b)
Marburg	Marburg hemorrhagic fever	Cynomolgus macaque	Hevey et al. (1998), Jones et al. (2005), Daddario-DiCaprio et al. (2006a)
Marburg	Marburg hemorrhagic fever	Guinea pig[a]	Hevey et al. (1998), Warfield et al. (2004)

[a] Virus adapted to produce lethal disease.

Development of a marmoset EBOV infection model is currently underway (J. Patterson, personal communication).

Guinea pigs have been used for preliminary evaluation of prophylactic and therapeutic measures against EBOV infection (Table 3). Connolly et al. (1999) developed a lethal guinea pig-adapted strain that produced pathologic and clinical disease manifestations very similar to those reported in experimentally infected macaques and human cases. One must use caution, however, when interpreting data from these animals, as treatment with a neutralizing monoclonal antibody shown to be effective in guinea pigs (Parren et al., 2002), failed to protect primates challenged with EBOV (Oswald et al., 2007). Similarly, EBOV has also been adapted to cause death in mice (Table 3). As with the guinea pig model, a number of antiviral therapies and vaccines that were effective in mice failed to protect nonhuman primates (Bray et al., 2002; Feldmann et al., 2003; Geisbert et al., 2002). Such findings have raised doubt as to the utility of rodent models for evaluating potential prophylactic and therapeutic strategies against EBOV infection. The inherent resistance of mice to wild-type EBOV appears to result from a highly effective type I interferon response (Bray, 2001). To this end, mice deficient in type I interferon responses might be better models for testing antiviral activity of drugs that target viral replication.

4.2. Marburg HF (MHF)

Similar to EBOV in most respects, Marburg virus (MARV) is also highly feared and considered to be one of the most dangerous of the VHF agents (Mahanty and Bray, 2004). Recent reemergence of MARV (Towner et al., 2006) has renewed interest in gaining a better understanding of pathogenesis to assist in the development of intervention strategies (Feldmann, 2006). As with EBOV, macaques are exquisitely susceptible to infection with MARV and develop severe disease closely reproducing MHF in humans (Table 3). Several studies evaluating vaccine strategies, including post-exposure prophylaxis, have been conducted using rhesus and cynomolgus macaques (Daddario-DiCaprio et al., 2006a,b; Jones et al., 2005). A guinea pig model also exists for MARV as a more accessible small animal model, which may be useful to study the disease and evaluate drug and vaccine candidates (Hevey et al., 1998; Warfield et al., 2004). Despite sharing principal features of disease with that caused by infection of humans and monkeys, adaptation by serial passage in the animals was required to make the virus lethal. Taking into consideration the lack of correspondence between experimental findings from efficacy studies wherein rodents and macaques were challenged with the closely related EBOV, results obtained with guinea pigs will certainly receive added scrutiny.

5. Flaviviral HF animal models

5.1. Dengue HF (DHF)

Infection with one of four dengue virus (DENV) serotypes results in an estimated 100 million cases of dengue fever (DF) and 500,000 cases of DHF each year, mostly in children under 15 years of age (Halstead, 1999). The incidence of DHF is 15–80 times higher in individuals after secondary infection with a heterologous DENV serotype, which may be due to enhancement of viral infectivity caused by non-neutralizing antibodies resulting from previous exposure to a different serotype, making model development very complicated. Efforts to develop a model of DHF have been ongoing for many years. To date three mouse models have been described (Table 4). The first is a humanized NOD-SCID mouse that has been xenografted with human $CD34^+$ cells, in which mice infected with DENV serotype 2 (DENV-2) develop characteristics of disease that are common in DHF such as thrombocytopenia, rash and a fever (Bente et al., 2005). A second model system employs mice lacking interferon-α/β/γ receptors and a serially passaged virus, in a system with disease characteristics that include evidence of increased vascular permeability (Shresta et al., 2006). The virus used in this system was derived from a very low passage DENV-2 isolate and was generated by serial passage through mosquito cells and mice. A third mouse model for DENV infection has recently been described that uses immunocompetent C57BL/6 mice and intradermal inoculation of extremely high titers of DENV-2 ($>10^9$ pfu) (Chen et al., 2007). In this system, the mice developed localized hemorrhages that were similar to those seen in DENV infection in humans, but unlike the previously described models, the disease was not systemic.

Table 4
Principal animal models for the study of flaviviral HFs

Virus	Disease modeled	Animal model	Selected references
Dengue	Dengue hemorrhagic fever	Mouse[a]	Shresta et al. (2006)
Dengue	Dengue hemorrhagic fever	Mouse[b]	Bente et al. (2005)
Dengue	Dengue hemorrhagic fever	Mouse[c]	Chen et al. (2007)
Yellow fever	Yellow fever	Rhesus macaque	Stephen et al. (1977), Monath et al. (1981)
Yellow fever	Yellow fever	Hamster[d]	Tesh et al. (2001), Xiao et al. (2001a), McArthur et al. (2003), Sbrana et al. (2004), Sbrana et al. (2006b), Julander et al. (2007b)
Omsk hemorrhagic fever	Omsk hemorrhagic fever	Mouse	Holbrook et al. (2005)
Kyasanur Forest disease	Kyasanur Forest hemorrhagic fever	Bonnet macaque	Kenyon et al. (1992)
Kyasanur Forest disease	Kyasanur Forest hemorrhagic fever	Mouse	Holbrook et al. (unpublished data)
Alkhurma hemorrhagic fever	Alkhurma hemorrhagic fever	No available model	

[a] Infection of mice lacking interferon-α, -β, and -γ receptors.
[b] Infection of humanized NOD-SCID mice xenografted with human CD34+ T cells.
[c] High challenge dose required with localized disease.
[d] Virus adapted to produce lethal disease.

Nonhuman primates are not effective for reproducing human dengue, as these animals do not develop clinical disease following infection. DENV is clearly unlike most other arboviruses that cause severe disease in humans in this respect, as most others will cause disease in nonhuman primates. DHF is considered an immune-mediated disease (Green and Rothman, 2006). In the vast majority of cases, patients do not seek medical attention during the initial phase of viral replication, but become severely ill only after immunopathogenesis is well underway. Although the recently described mouse models should provide insights into antiviral activities of experimental drugs that target viral replication, efficacy in these models may not be relevant to the treatment of severe human disease. With the objective of simulating DHF in humans, the major immunopathological component of the disease will make future animal model development extremely difficult, which could hinder the production of vaccines and therapeutics, if the "Animal Rule" for FDA acceptance of agents cannot be met (Roberts et al., 2008).

5.2. Yellow fever (YF)

Yellow fever virus (YFV) is a flaviviral HF agent that infects an estimated 200,000 people annually in regions in South America and Africa and accounts for around 30,000 deaths, despite the availability of an effective vaccine (Monath, 2008). Most infections result in a self-limiting febrile illness, but approximately 15–30% of infected individuals will enter into a more serious toxic phase (~50% case fatality), and may present with jaundice, renal failure, vascular leakage, and shock (Tomori, 2004). Like DENV, yellow fever virus (YFV) does not cause disease in mice more than 8 days old and infection of suckling mice results in neurological disease that is very dissimilar to the disease seen in humans. However, unlike DENV, YFV causes severe disease in rhesus macaques that is similar to that seen in humans (Monath et al., 1981; Stephen et al., 1977), making the nonhuman primate model a valid system with potential for antiviral studies (Table 4). Extensive studies of YFV pathogenesis using this system have not been pursued.

Several years ago two different models of YF were described in which viruses were adapted to hamsters by serial passage (Table 4). Tesh et al. (2001) used the Jimenez strain of YFV while McArthur et al. (2003) used the more extensively characterized Asibi strain of YFV. Infected hamsters were found to have elevated liver enzyme values, increased coagulation times, thrombocytopenia and lymphopenia, with pathological findings of microvascular steatosis, apoptosis and necrosis in the liver (McArthur et al., 2003; Sbrana et al., 2006b; Tesh et al., 2001; Xiao et al., 2001a). There was also significant evidence of viral antigen in the liver indicating that the virus is directly causing the hepatic injury in infected hamsters. In both systems, the pathology is similar to that seen in humans, making them viable models for development of therapeutics for treatment of YF. Several antiviral evaluations have recently been conducted employing these models (Julander et al., 2007a,b; Sbrana et al., 2004).

5.3. Omsk HF (OHF)

OHF has a limited endemic range confined to the Omsk and Novosibirsk Oblast region in Siberia, Russia. The virus causes a febrile illness with occasional indications of HF. It has been isolated from a wide range of animals and arthropods (Kharitonova and Leonov, 1985) with voles thought to be the primary host. The only established animal model is the mouse (Table 4), in which OHFV causes a lethal disease that is largely devoid of neurological signs (Holbrook et al., 2005). Despite the lack of clear neurologic disease, OHFV does invade the brain late in the infection and primarily targets Purkinje cells in the cerebellum. Other small animals, particularly muskrats, are known to be susceptible to infection (Kharitonova and Leonov, 1985). Productive infection of bonnet monkeys with OHFV has been attempted but the virus was effectively cleared with no apparent disease (Kenyon et al., 1992).

5.4. Kyasanur forest disease (KFD)

KFDV is a tick-borne flavivirus that causes a hemorrhagic disease in humans. KFDV can also cause encephalitis, so the pathogenesis of this illness is quite different from DHF and YF. Unlike DENV and YFV, but similar to OHFV, KFDV causes

a lethal disease in mice following peripheral challenge, but its pathogenesis is not well characterized (Holbrook et al., unpublished data). In its natural environment, KFDV causes severe or fatal disease in wild primates, which is often associated with the onset of human outbreaks. A nonhuman primate model to study KFD has been described in bonnet macaques (Table 4). Infection was evident primarily in gastrointestinal and lymphoid tissues (Kenyon et al., 1992). In other nonhuman primates infected with KFDV, encephalitic lesions have been observed (Webb and Chaterjea, 1962).

A closely related flavivirus, Alkhurma virus (ALKV), has been recently identified as the agent of a VHF infrequently diagnosed in Saudi Arabia (Charrel et al., 2005). At the genetic and serologic levels, similarities between ALKV and KFDV have led to its description as variant genotype of KFDV (Charrel et al., 2001). No animal models have yet been developed to study this disease. Nevertheless, the relatedness of this virus to KFDV suggests that models applicable to the study of KFD may be relevant to ALKV infections.

6. Concluding remarks and future directions

One of the greatest challenges facing the development of effective countermeasures for the treatment of severe human diseases such as VHFs is the accurate modeling of the infection and disease state in animals so that prophylactic and therapeutic interventions tested experimentally will actually serve to predict efficacy in humans. In addition to nutritional status and underlying infections, the genetic differences associated with the highly outbred human population are just a few of the many factors that complicate the study of human diseases through animal models. These and other environmental factors presumably influence the spectrum of disease produced by VHF agents, where infection of an individual can lead to various forms of disease ranging from mild febrile illness to full-blown HF, with or without late-onset encephalitis. The latter may be due to immunopathological events, and, thus, even a highly effective antiviral will be of little efficacy once the illness has progressed to encephalitis. Along these lines, drugs that directly block viral replication would be expected to be effective early in the course of many illnesses, but patients are usually identified only after their disease has progressed to the point that host responses are responsible for the major features of illness. Therefore, effective therapies will likely consist of antiviral treatment to reduce viral burden combined with drugs that help control the deleterious host responses that drive the disease.

Undoubtedly, nonhuman primates are the most relevant models for the study of VHFs, because they most closely mimic human host responses. However, small animal models are also essential, in that they can provide valuable preclinical information, such as oral bioavailability of a drug and the frequency of dosing required for efficacy, prior to advancing an experimental treatment into the considerably more costly and restrictive primate models. Such models are most likely to predict efficacy in nonhuman primates when used to test drugs that directly inhibit steps in viral replication. Although mouse models are widely used in infectious disease research, hamsters and guinea pigs have proven especially useful in studying some types of VHF. The biggest limitation is a lack of reagents available for work in these species, particularly with respect to immune responses to infection. The increased interest in the hamster model for many viral infections should stimulate the commercial production of appropriate reagents.

In addition to animal models employing HF viruses, the use of surrogate viruses to study disease can also be a viable option. The reduced cost associated with working with such models facilitates early stage drug development and can be useful in working out various parameters such as effective concentrations, dosing frequencies, and route of administration prior to moving into higher order species models based on infection with actual VHF agents. Antiviral studies conducted using PTV (Sidwell et al., 1994; Sidwell et al., 1988b) and PICV (Lucia et al., 1989; Smee et al., 1993) infection models suggest that they may be able to predict efficacy against their related HF viruses in humans (Jahrling et al., 1980; Peters et al., 1986). Nevertheless, one must use greater caution when interpreting results employing surrogate virus-based models, because differences in pathogenesis and viral proteins targeted for antiviral intervention may affect the translation of the results to humans. It is important to note that with the increasing number of high-containment laboratories coming into operation, research with models based on infection with authentic VHF pathogens will likely accelerate.

The availability of multiple animal models is critical to drug development for low-incidence viral diseases such as many of those considered in this review. Because clinical trials would not be feasible in most cases, FDA approval as an indication for treatment will require meeting the “Animal Rule” (Roberts et al., 2008). Under this provision, a candidate antiviral or vaccine could be licensed to treat an infrequent disease if it is proven safe in humans and if adequate protection can be demonstrated against a deliberate infectious challenge in preferably two species of animals wherein the results would be predictive of the human response. Unfortunately, the implementation of these criteria in low-incidence diseases of viral or non-viral origin and the increase in biodefense funding to gain a better understanding of many of these diseases in the most well-characterized and predictive nonhuman primate models has contributed to a current shortage of macaques for research (Patterson and Carrion, 2005). The development and use of the much smaller marmoset models may help to ease this burden, and will also redefine the term “small animal”, since these monkeys are equivalent in size to a guinea pig. The marmoset models may be especially useful for evaluating promising antiviral drugs. The utility of such models for understanding viral pathogenesis and the host response to infection will depend largely on the availability of suitable reagents, which are currently not up to par with the macaque systems.

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