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Review

Animal models of mpox virus infection and disease

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ABSTRACT

Mpox (monkeypox) virus (MPXV), which causes a mild smallpox-like disease, has been endemic in Africa for several decades, with sporadic cases occurring in other parts of the world. However, the most recent outbreak of mpox mainly among men that have sex with men has affected several continents, posing serious global public health concerns. The infections exhibit a wide spectrum of clinical presentation, ranging from asymptomatic infection to mild, severe disease, especially in immunocompromised individuals, young children, and pregnant women. Some therapeutics and vaccines developed for smallpox have partial protective and therapeutic effects against MPXV historic isolates in animal models. However, the continued evolution of MPXV has produced multiple lineages, leading to significant gaps in the knowledge of their pathogenesis that constrain the development of targeted antiviral therapies and vaccines. MPXV infections in various animal models have provided a central platform for identification and comparison of diseased pathogenesis between the contemporary and historic isolates. In this review, we discuss the susceptibility of various animals to MPXV, and describe the key pathologic features of rodent, rabbit and nonhuman primate models. We also provide application examples of animal models in elucidating viral pathogenesis and evaluating effectiveness of vaccine and antiviral drugs. These animal models are essential to understand the biology of MPXV contemporary isolates and to rapidly test potential countermeasures. Finally, we list some remaining scientific questions of MPXV that can be resolved by animal models.

1. Introduction

Mpox (Mpox) is a neglected zoonosis caused by the mpox virus (MPXV), a double-stranded DNA virus in the genus *Orthopoxvirus* of the family *Poxviridae*, which also includes several other pathogens of public health importance, such as variola virus, vaccinia virus, cowpox virus, and camelpox virus [1–3]. MPXV was first discovered in 1958 from a diseased laboratory monkey in Copenhagen, Denmark, and the first human case occurred in 1970 in a child in the Democratic Republic of Congo (DRC) [4]. Since then, mpox has been reported as a zoonosis endemic in Western and Central Africa, including DRC, Liberia, Gabon, Sierra Leone, Cameroon, Nigeria, and the Central African Republic [5–9]. However, sporadic cases of mpox have occurred outside Africa, such as the United States of America [10–12], the United Kingdom [13], Israel [14], and Singapore [15]; these diseases are associated with traveling to Africa or with infected animals imported from Africa.

The natural reservoirs of MPXV are still not completely determined, though MPXV has been isolated from *Funisciurus anerythrus* and *Cercocebusatys*, and a variety of wild animal species, such as rodents and nonhuman primates (NHPs), have been demonstrated to be susceptible to the virus [16,17]. Human can be infected with MPXV via direct contact with infected animals or contaminated objects, scratching or biting by animals, or eating meat from infected animals [18], and nosocomial and household transmission has also been described [13,19]. As reviewed elsewhere [20,21], the most common clinical symptoms of MPX are fever, rash headache, chills,

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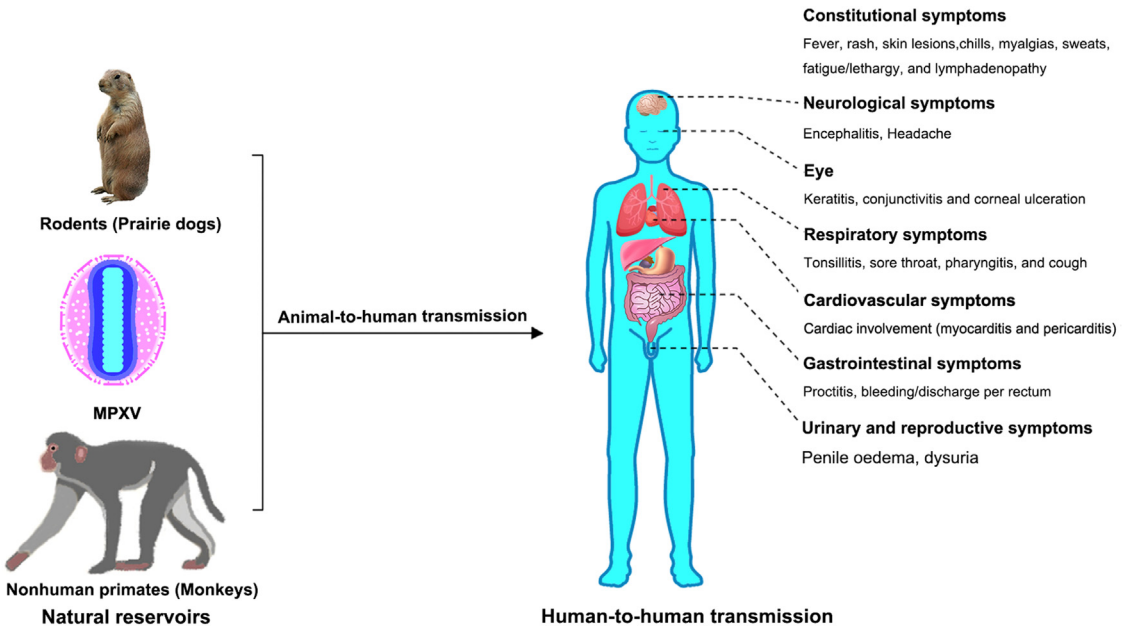

Fig. 1. The clinical features of mpox virus (MPXV) infection in humans. MPXV circulates among natural reservoirs in sylvatic cycle, and human can be infected by animal-to-human and human-to-human transmission, and most infections occurred through sexual contact in the current MPXV outbreak. The infections exhibit a wide spectrum of clinical presentation, ranging from asymptomatic infection to mild, severe disease, especially in young children, pregnant women and immunocompromised individuals, characterized by constitutional symptoms of fever, rash, skin lesion, chills, myalgias, sweats, fatigue, lethargy, and lymphadenopathy, and involved in neurological, eye, respiratory, cardiovascular, gastrointestinal, urinary, and reproductive systems.

lethargy, muscle/joint pain, fatigue, and swollen lymph nodes, which are similar to smallpox, but milder, with a case fatality rate (CFR) of approximately 1%–10% (Fig. 1) [22,23]. However, a high CFR of 14.9% was reported in young children less than 4 years old [24]. MPXV can be vertically transmitted from mother to fetus in pregnant woman, leading to miscarriage and stillbirth [25].

Recently, MPXV has rapidly spread across Europe and North America. Since first report of MPVX cases in the United Kingdom in early May 2022, more than 86,930 confirmed case and 116 deaths had emerged in at least 100 countries/territories by 13 April, 2023 (https://ourworldindata.org); most cases had no clear epidemiological links to the endemic countries, suggestive of potential community transmission of MPXV. Of note, a clinical investigation involving in 528 human MPXV in 16 countries during April–June, 2022 showed that 98% of patients were gay or bisexual men, and 95% infections occurred through sexual contact [26]. The ongoing mpox outbreak has been declared a Public Health Emergency of International Concern by the World Health Organization.

Phylogenetically, MPXV is divided into the Congo Basin (CB) and West Africa (WA) clades; the CB clade is more virulent than the WA clade, whereas the WA clade is more common and is associated with the outbreaks in the USA, Nigeria, and several travel-related cases in nonendemic countries. Up to now, all available MPXVs from the 2022 MPX outbreak have been confirmed to belong to the WA clade, but evolved into multiple lineages, leading to the concern of an emerging global pandemic [27,28]. Several therapeutics and vaccines developed for smallpox have partial protective and therapeutic effects against MPXV historic isolates in animal models (Table 1). There are still significant gaps in the knowledge of their pathogenesis that constrains the development of targeted antiviral therapies and vaccines. MPXV infections in various animal models have provided a central platform for identification and comparison of disease pathogenesis between contemporary and historic isolates. In this Review, we discuss the susceptibility of various animals to MPXV, and describe the key pathologic features of infection models. We also provide application examples of animal models in elucidating viral pathogenesis and evaluating effectiveness of vaccine and antiviral drugs, which are essential to understand the biology of MPXV contemporary isolates and to rapidly test potential countermeasures.

2. Mouse model

Mice are the most widely used infection models for a spectrum of viruses, including coronaviruses, flaviviruses, filoviruses, as they have many advantages, including the commercial availability, genetic homogeneity, well-characterized immune system, high reproduction capability, and a large variety of immunological reagents available [29–31]. The vast majority of *in vivo* MPXV infections have been conducted in mice to develop an ideal animal model (Fig. 2). The mouse strain, age, immune status, infection route, and inoculation dose greatly affect the severity and outcomes of the infection of MPXV. Most adult mouse strains infected with MPXV show no clinical

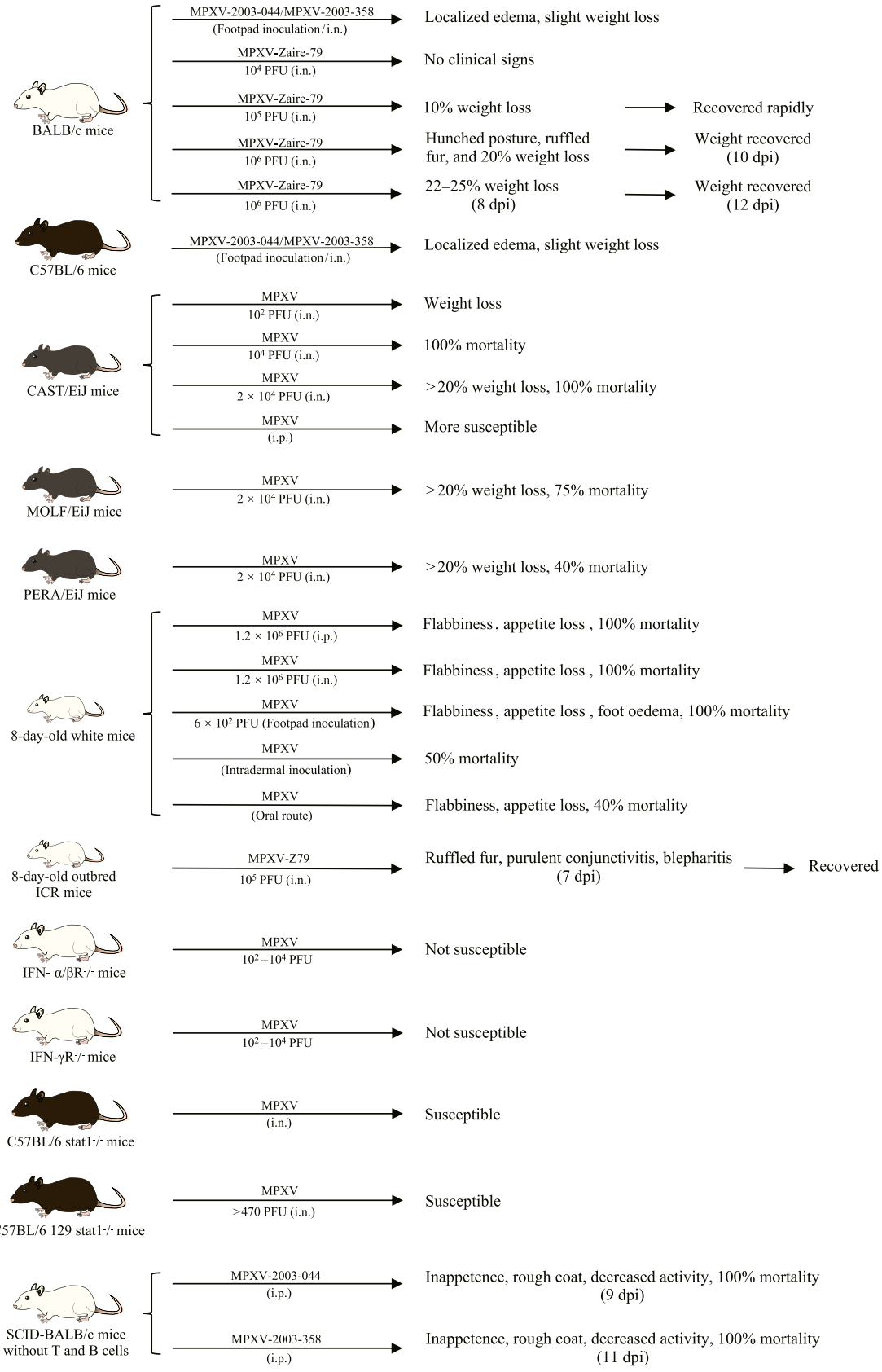

Fig. 2. The mouse models for MPXV. i.n., intranasal infection; i.p., intraperitoneal infection.

Table 1
Mpox viruses used in animal infection.

Virus strain	Viral clade	Virus source	Reference
MPXV-2003-044 (DQ011153.1)	WA[a]	An infected prairie dog associated with the index human case in the United States during the 2003 outbreak	Likos et al. [32]
MPXV-2003-358 (DQ011154.1)	CB	A 10-year-old girl in the Republic of Congo (ROC) in 2003	Likos et al. [32]
Zaire-79 (HQ857562.1)	CB	A fatal human case in Zaire in 1979	Breman et al. [5]
SP2833 (ON880519.3)	WA	A lesion swab collected from a laboratory-confirmed case of mpox in Canada during the 2022 outbreak	Warner et al. [33]
Copenhagen (AJ315001.1)	CB	A diseased laboratory monkey in Copenhagen, Denmark in 1958	Jezek et al. [4]
Zr-599 (AB371718.1, AB371719.1, AB371720.1, AB371721.1)	CB	A patient with MPX in the Democratic Republic of Congo	Saijo et al. [34]
COP-58 (AY753185.1)	WA	The cynomolgus macaques in 1958	Von Magnus et al. [35]

[a] WA, West Africa clade; CB, Congo Basin clade

Table 2
Comparison of susceptibility of different mouse strains to mpox virus.[a]

Mouse strain	Weight loss (%)	Mortality (%)
129S1/SvlmJ	5.2	0
A/J	5.4	0
BALB/cByJ	0	0
C/HeJ	0	0
C57BL/6J	3.6	0
DBA/2J	0	0
CAST/EiJ (WD)	23.3	100
DBA/2J	0	0
FVB/NJ	0	0
SJL/J	0	0
SPRET/EiJ (WD)	0	0
AKR/J	0	0
C57L/J	0	0
C58/J	14.4	0
MOLF/EiJ (WD)	21.3	75
NOD/ShiLtJ	0	0
NZB/BINJ	0	0
PERA/EiJ (WD)	24.8	40
PL/J	9.1	0
SM/J	0	0
SWR/J	3.5	0
BUB/BnJ	0	0
C57BL/10J	3.1	0
C57BLKS/J	8.5	0
CBA/J	0	0
CZECHII/EiJ (WD)	2.8	0
LP/J	0	0
RIIIS/J	0	0
WSB/EiJ (WD)	0	0
BTBR T^+ tf/J	0	0
C57BR/cdJ	0	0
CE/J	0	0
I/LnJ	0	0
MA/MyJ	0	0
NON/ShiLtJ	0	0
NZW/LacJ	14.1	0
PWK/PhJ (WD)	7.7	0
SEA/GnJ	2.6	0
BALB/c	0	0

[a] Animals were infected intranasally with 2×10^4 PFU MPXV Zaire-79 [36].

signs and little to no viral RNA in wild-type mice, with the exception of 3 wild-derived inbred strains, including CAST/EiJ, MOLF/EiJ, and PERA/EiJ mice [36]. However, sucking and immunocompromised mice are susceptible to MPXV infection (Tables 2 and 3) [37].

2.1. Adult mice

Both BALB/c and C57BL/6 mice infected with the MPXV-2003-044 or MPXV-2003-358 strains of MPXV did not develop clinical diseases as observed those in humans, only appeared localized edema with the footpad inoculation and slight weight loss with the intranasal infection [38]. BALB/c mice infected intranasally (i.n.) with 10^6 plaque forming unit (PFU) of MPXV Zaire-79 showed hunched posture, ruffled fur, and weight loss of approximately 20%; however, the lost weight was recovered 10 days postinfection (dpi); animals infected with 10^5 PFU exhibited weight loss of only 10% that was recovered rapidly; while the animals injected with 10^4 PFU or less presented no clinical signs [39]. By comparison, BALB/c mice infected i.n. with 10^7 PFU MPXV Zaire-79 had weight loss of 20%–25% by day 8, which was completely recovered by 12 dpi [39]. The resistance of BALB/c mice to MPXV infection is associated with the induction of IFN-γ [39]. In these experiments, no animals infected with MPXV died, leading to a high value of the median lethal dose (LD_{50}) of 10^7, which is impractical to investigate pathogenicity of MPXV.

Further susceptibility analysis of mouse strains to MPXV showed highly susceptible wild-derived CAST/EiJ, MOLF/EiJ, and PERA/EiJ; these animals at the dose of 2×10^4 PFU by i.n. infection exhibited >20% weight loss and a mortality of 100%, 75%, and 40%, respectively [36]. CAST/EiJ mice had a dose response to i.n. infection of MPXV, showing some clinical signs and weight loss at 10^2 PFU, and 100% mortality at 10^4 PFU. Moreover, CAST/EiJ mice were more susceptible to MPXV infection by the intraperitoneal (i.p.) route, with a low LD_{50} of 14 PFU. However, no significant skin lesions were seen in the both inoculation routes. MPXV was mainly distributed in the lung, liver, and spleen tissues in infected animals, with higher titer in the lung after i.n. inoculation and a higher titer in the liver and spleen after i.p. administration. Additionally, a high viral titer was also detected in the ovaries of all animals, independent of the infection doses [36]. In contrast, footpad inoculation only led to mild weight loss and localized leg swelling [36].

Lethal MPXV infection in CAST/EiJ mice is associated with a deficient interferon-gamma (IFN-γ) response [39], which has been demonstrated by the intranasal administration of the cytokine to the animals to protect against MPXV infection. IFN-γ is induced in BALB/c mice infected

Table 3
Animal models of mpox virus.

Model and strain or animal (age)	Inoculation routes	Clinical feature	Virus (infection dose)	References
CAST/EiJ mice (WD)	Intranasal	100% lethality, weight loss of 20–30% at doses of 10^3 PFU; virus detected in lung, spleen, brain and kidney; LD_{50} of 680 PFU for MPXV Zaire-79; LD_{50} of 7,600 PFU for MPXV-2003-044	MPXV Zaire-79, MPXV-2003-044	Americo et al. and Earl et al. [36,39]
BALB/c mice	Intranasal	No mortality; transient weight loss; virus detected in lung, spleen, brain, kidney	MPXV Zaire-79 (up to 10^6 PFU)	Earl et al. [39]
MOLF/EiJ (WD, inbreed)	Intranasal	70% lethality; weight loss of 21.3%	MPXV Zaire-79 (2×10^4 PFU)	Americo et al. [36]
PERA/EiJ (WD)	Intranasal	40% lethality; weight loss of 24.8%	MPXV Zaire-79 (2×10^4 PFU)	Americo et al. [36]
C57BL/6 stat1$^{-/-}$	Intranasal	90–100% mortality	MPXV Zaire-79 (470–4,700 PFU)	Stabenow et al. [40]
SCID-BALB/c	Intraperitoneal	100% lethaligy; virus detected in ovary, lung, heart, liver, kidney, and pancreas	MPXV-2003-044, MPXV-2003-358 (10^5 PFU)	Osorio et al. [41]
African rope squirrels (*Funisciurus*)	Intranasal and intradermal	50–70% lethaligy; pox lesions dyspnea, and profuse nasal discharge; high levels of viremia, fast systemic spread, and prolonged viral shedding	MPXV-2003-358 (10^6 PFU)	Falendysz et al. [42]
Prairie dogs (*Cynomys ludovicianus*)	Intraperitoneal, intranasal	60–100% mortality	MPX-2003-044 ($10^{5.1}$ PFU)	Xiao et al. [43]
Ground squirrels (*Spermophilus tridecemlineatus*)	Intraperitoneal, intranasal	100% lethality, lethargic and anorexic; virus detected in blood, throat swab, liver, spleen, kidney, lung, heart and brain	MPX-2003-044 ($10^{5.1}$ –$10^{6.1}$ PFU)	Tesh et al. [44]
African dormice (outbreed)	Intranasal	100% mortality; general disease with necrosis and hemorrhage; virus detected in nasal lavages, spleen, liver, lung and blood	MPXV Zaire-79	Schultz et al. [45]
Rabbit (adult)	Intravenous	8% lethality; general disease with fever and rash; virus detected in blood, lymph nodes, kidney and testicle	Copenhagen (10^7 PFU)	Marennikova et al. [37]
Rabbit (adult)	On scarified skin	Local eruption, fever, rash on the skin and mucous membranes	Copenhagen (10^5–10^6 PFU)	Marennikova et al. [37]
Rabbit (adult)	Intradermal	Dense infiltration with necrosis	Copenhagen (10^5–10^6 PFU)	
Rabbit (10 days)	Intranasal, oral	83–85% mortality; weight loss, adynamia, acute general disease with rash; virus detected in blood, lung, liver, and spleen	Copenhagen (10^6–10^7 PFU)	Marennikova et al. [37]
White mouse (8 days)	Intranasal, intraperitoneal, intradermal, oral, footpad	24–100% lethality with different infection routes; weight loss, adynamia, local infiltration, foot oedema, general disease; virus detected in blood, lung, liver, spleen and kidney	Copenhagen (1.2×10^6 PFU)	Marennikova et al. [37]
Newborne white rat (1–3 day(s))	Intranasal	100% lethality; adynamia; virus detected in lung and liver	Copenhagen (100 PFU)	Marennikova et al. [37]
Guinea-pigs	Foodpad	Food oedema	Copenhagen	Marennikova et al. [37]
Cynomolgus monkeys (*Macaca fascicularis*)	Aerosol	aerosol inhaled doses of 10,000–141,000 PFU caused 100% lethality associated with severe fibrinonecrotic bronchopneumonia.	MPXV Zaire-79 (2×10^4 PFU)	Zaucha et al. [46]
Rhesus macaques	Intravenous	Low dose (5×10^6 PFU) caused disseminated exanthema and animals survived. High dose (5×10^8 PFU) caused organ-hemorrhagic and all animal died on day 6 postinfection; virus detected in lymph nodes, heart, lungs, urinary bladder, uterus, and digestive tract.	MPXV Zaire-79 (5×10^8 PFU)	Hooper et al. [47]
Marmosets (*Callithrix jacchus*)	Intranasal	an incubation period of approximately 13 days, followed by the onset of rash, and death between 15 and 17 days.	MPXV Zaire-79 (1,000 PFU)	Mucker et al. [48]
Marmosets (*Callithrix jacchus*)	Intravenous	Generalized erythema present in animals at higher doses; more focal/discrete hemorrhages at lower doses.	MPXV Zaire-79 (more than 48 PFU)	Mucker et al. [49]

WD, wild derived; LD50, 50% lethal dose.

with MPXV, but not in CAST/EiJ mice. If the IFN-γ gene or the IFN-γ receptor gene was inactivated, C57BL/6 mice exhibited enhanced sensitivity to MPXV [39]. MOLF/EiJ mice exhibited decreased secretion of tumor necrosis factor (TNF) upon poly (I:C) stimulation, a synthetic double-stranded RNA analog [50,51]. PERA/EiJ mice also lack the type I cytokine (IL-12) response and a concomitant failure to maintain virus-specific cytotoxic T lymphocytes [52]. These results may explain why the immunocompetent animals are generally resistant to MPXV infection.

The CAST/EiJ mice have many advantages as a model, such as high sensitivity to MPXV, genetic homogeneity, commercial production and available immunological reagents, and may be useful to investigate pathogenesis of MPXV and to evaluate potential vaccines and therapeutics [33].

2.2. Neonatal mice

MPXV infection has been conducted in wild-type neonatal mice. Intraperitoneal (1.2×10^6 PFU), intranasal (1.2×10^6 PFU) and footpad (6×10^2 PFU) inoculation of MPXV caused 100% mortality in 8-day-old white mice, with the main symptoms of flabbiness, appetite loss and foot oedema (after footpad inoculation). Intradermal inoculation resulted in infiltrates, with a mortality of 50%

[37]. Mice inoculated by the oral route became flabby and lost appetite, and 40% of them died. A lower LD_{50} was found in 8-day-old mice by intranasal inoculation as comparison with the animals by oral inoculation, showing higher sensitivity of neonatal mice with the intranasal infection, which was also confirmed by the inoculation of older animals. The 12-day-old mice infected orally sickened and died in only 14% of cases, whereas 100% mortality was seen in 15-day-old mice after intranasal inoculation with the same viral dose. The virus could be isolated from the blood after one week and from the lung, liver, spleen, and kidney tissues after 3 weeks of oral inoculation. A considerable amount of virus was detected in the lung and other organs at the acute infection stage as a result of intranasal inoculation [37].

The 8–10 days-old outbred ICR mice showed a certain susceptibility to MPXV at a high dose for i.n. challenge with 10^5 PFU MPXV Zaire-79, whose clinical signs of ruffled fur, purulent conjunctivitis, and blepharitis occurred 7 dpi, and disappeared after 11–13 dpi; and the maximum accumulation of MPXV was found in nasal cavity, lung, and brain [53]. The primary target cells were involved in mononuclear phagocyte cells, respiratory tract epitheliocytes, endothelial cells, connective tissue cells, and reticular cells.

As the key brain developmental processes occur postnatally in rodents, neonatal mice have been widely used as models for neurotropic viruses, including Zika virus and dengue virus. MPXV can cause the neurologic manifestations in humans [54], the neonatal mice may thus be useful models to investigate mechanism of nervous system lesions of MPXV. However, the immunoimmature animals cannot be used as ideal models for immune responses, antiviral and vaccination efficacy studies of MPXV infection.

2.3. Immunocompromised mice

IFN signaling is the first defense line against viral infection, and mice with deficient IFN signaling have high susceptibility to virus infection. Accordingly, as the classic inbreed mice are resistant to MPXV infection, several groups have evaluated the capacity of immunocompromised mice to support MPXV infection or disease. However, IFN-$\alpha/\beta R^{-/-}$ and IFN-$\gamma R^{-/-}$ mice were not susceptible to MPXV at the doses of 10^2–10^4 PFU. In contrast, the severe combined immune deficient (SCID) mice, C57BL/6 *stat1*$^{-/-}$ and 129 *stat1*$^{-/-}$ strains are susceptible to an intranasal MPXV infection, due to a lack of type I or II IFN-induced STAT1-dependent signaling pathways.

MPXV infection can caused 100% lethality in SCID-BALB/c mice without T and B cells. Intraperitoneal injection caused a systemic clinical disease of inappetence, rough coat, and decreased activity, and death occurred at 9 dpi for MPXV-2003-358, and at 11 dpi for MPXV-2003-044, respectively [41]. In SCID-BALB/c mice, MPXV-2003-358 was limited to the peritoneal cavity as early as 24 hours postinfection, and spread to other tissues in the thoracic and abdominal areas, and axillary lymph nodes by 4 dpi. In SCID mice infected with MPXV-2003-044, virus was also detected in the abdominal region at 4 dpi, and found in the feet, tail, and nasal area at 10 dpi. Viral titers in the ovaries were detected about 100-fold higher than in other tissues for both the MPXV-2003-044 and MPXV-2003-358 strains, suggesting that the ovary may be an important target for viral replication of MPXV [41]. However, the severely compromised immune system of SCID mice limits their practical application as an animal model.

The signal transducer and activator of transcription 1 (STAT1) is a key protein involved in the IFN signaling [55], and STAT1-knockout mice are highly susceptible to a number of viruses and bacteria, and have been used to develop several disease models, including severe acute respiratory syndrome-associated coronavirus [56], Chlamydia pneumoniae [57], and Mycobacterium tuberculosis [51]. The 129 *stat1*$^{-/-}$ mice showed some sensitivity to intranasal MPXV infections with higher doses than 470 PFU; however, the C57BL/6 *stat1*$^{-/-}$ strain was highly susceptible to the infection, with LD_{50} values of 47 and 213 PFU for males and females, respectively. The higher LD_{50} for females can be due to their propensity to produce a high level of IFN-γ. The differences in sensitivities of 129 *stat1*$^{-/-}$ and C57BL/6 *stat1*$^{-/-}$ strains indicate that strain, background, and gender-specific alleles may have an important role in the host susceptibility to virus infection. Moreover, the *stat1* mutation is different between the mouse strains, as no detectable STAT1 is expressed in the C57BL/6 *stat1*$^{-/-}$ strain, whereas a limited amount of STAT1 is expressed in the 129 *stat1*$^{-/-}$ strain, which may be associated with its decreased viral sensitivity [58,59]. Cells and tissues from *stat1*$^{-/-}$ mice are unresponsive to IFN, but remain responsive to other cytokines; this model can thus be used in vaccine and antiviral efficacy trials [40,60].

The role of IFN-γ against MPXV infection has been demonstrated by CAST/EiJ mice i.n. injected with the cytokine to produce protection against MPXV infection, and C57BL/6 mice inactivating IFN-γ or its receptor gene to enhance sensitivity to MPXV infection [39].

3. Rat model

MPXV infection has been studied in several rat species, such as white rats, multimammate rats, and cotton rats [61]. Adult white rats infected with WA strain of MPXV showed no clinical symptom through intravenous, intranasal, or cutaneous inoculation routes, and the virus was not isolated from the blood and viscera of these rats [37]. However, newborn white rats of 1–3 days old de-

veloped adynamia, death occurred in 5–6 days when i.n. challenged with MPXV; the virus was not cultured from their lung and liver tissues [37]. Multimammate rats were shown susceptible to both i.n. and i.p. infection with MPXV.

Cotton rats (*Sigmodon hispidus*) have been shown to be susceptible to MPXV infection. When cotton rats were i.v. challenged with 10^5 PFU MPXV, 100% mortality was observed 4–5 dpi, characterized by difficult breathing, sneezing, cough, cyanosis, purulent conjunctivitis, rhinitis, and progressive emaciation. Intranasal MPXV challenge in cotton rats caused a mortality of 50% [62–64]. Additionally, cotton rats have been proven a suitable small animal model for measles virus and respiratory syncytial virus [61,65]. The available inbred cotton rats and relevant commercial reagents thus provide another small animal model for MPXV research [61].

4. Guinea pigs

The susceptibility of guinea pigs to MPXV was determined by oral, intranasal, intracardial, and footpad inoculation routes. No clinical symptom was seen in the animals infected by these methods, with the exception of foot oedema after footpad inoculation [37]. Virus could only be detected in the lung tissues 7 days after intracardial inoculation, but it was not traceable 14 dpi. Guinea pigs inoculated by the intranasal and intracardial footpad routes could produce haemagglutination-inhibiting antibodies [37].

5. Hamsters

Hamsters can be used as a model of severe acute respiratory syndrome (SARS) coronavirus-2 and hantavirus pulmonary syndrome [66,67]. No symptom of the disease was seen in hamsters infected mpox orally, by the intranasal and intracardial routes, or on the scarified skin ($1.5–5.9 \times 10^7$ PFU). Nevertheless, significant pathological alterations were observed in the viscera of hamsters inoculated with mpox by the intracardial route and the virus was also detectable [37].

6. Wild rodents

In 2003, several wild rodent species that were imported from Ghana were associated with the MPXV outbreak in the United States, and *Cricetomys, Graphiurus*, and *Funisciurus* have been demonstrated to be infected with MPXV, suggesting an important role in transmission of MPXV to humans and to other animals [68,69].

6.1. African dormouse (Graphiurus kelleni)

African dormouse, *Graphiurus kelleni*, is a native mouse-sized rodent in the African continent, where human MPX is endemic. Experimentally, African dormice was susceptible to MPXV, as the animals inoculated with 1.4×10^4 PFU of MPXV Zaire-79 via a footpad route produced a mortality of 92%; the intranasal infection of 200–2,000 PFU resulted in 100% mortality; 20 PFU produced 63% mortality, and 2 PFU had 38% mortality, while no mortality was seen at 0.2 PFU. The LD_{50} of MPXV Zaire-79 in dormice by the i.n. infection was 12 PFU [36,45]. The main clinical signs included adynamia, hunched posture, dehydration, unkempt hair coat, and conjunctivitis. Viral DNA was firstly detected in nasal lavages 2 dpi, followed by detection in the blood, lung, spleen, and liver 3–4 dpi, suggesting that the lung may be infected with the virus by the lymphatic and hematogenous spread. Histopathological findings showed upper gastrointestinal hemorrhage, hepatomegaly, and lymphadenopathy, including rhinitis, lymphoid necrosis and hepatocellular necrosis, and hemorrhage in the lung, stomach, and small intestine. In dormice found dead, hemorrhage was also found in the nasal cavity, gall bladder, and brain. Dormice can be used to evaluate prophylactic and therapeutic effects of vaccines and drugs against intranasal challenges with MPXV [45]. Compared to CAST/EiJ mice, dormice showed a greater variation of viral spread, short course of disease, low virus titers in brain and chest, and high virus titers in abdominal organs [70].

The MPXV-dormouse model can recapitulate the hemorrhagic smallpox subtype, which has a more severe disease than other rodents. Severe necrosis of liver and bone marrow may result in reduced coagulation ability, as platelets and clotting factors have been lost, and the multiorgan hemorrhage leads to damage of endothelium in affected tissues [45]. The mechanisms for severe hemorrhage in dormice remain to be investigated.

When compared with other rodents, dormice have similar traits to those of laboratory mice, thus enabling the successful maintenance and propagation within a research vivarium, allowing for an accessible supply with a determined health assess, and easily utilizing customary rodent caging. Cidofovir and Dryvax vaccine can protect against a lethal MPXV Zaire-79 infection in this model, supporting that the dormouse may be a useful animal model for pathogenesis, vaccine and therapeutic studies of MPXV.

6.2. Ground squirrels

African rope squirrels (*Funisciurus anerythrus*), where human mpox had been reported, can be naturally infected with MPXV [16,71]. Infection with 10^6 PFU of MPXV-2003-358 by intradermal (i.d.) and i.n. routes caused mortality of 50–70% in African rope squirrels, which exhibited moderate to severe disease, with clinical signs of dyspnea, nasal discharge, and pox lesions in the nose, mouth, eyes, and skin. Both i.n. and i.d. exposures caused

a high level of viremia, long period of viral shedding and fast systemic spread. Viral shedding peaked at 6 pdi, and was still detectable after 15 dpi. Interestingly, an animal that was housed in the same room, but in a separate cage, also had severe clinical disease of MPXV [42], indicating that MPXV infection can cause significant disease in African rope squirrels that shed large quantities of virus, suggestive of an important role of the animal species as a potential infection source of MPXV in endemic regions.

It has been demonstrated that 50% of the infective dose (ID_{50}) of MPXV (Zaire-79) on external clinical symptoms of the disease was $10^{2.2}$ PFU for *Marmota bobak* [72]. Animals infected with MPXV by i.n. challenge exhibited pox-like clinical disease 7–9 dpi, such as lymphadenitis, hyperthermia, rash all over the body, and some diseased animals (about 40%) died 13–22 dpi [73]. A high virus titres were tested in the nasal mucosa, trachea, lung, kidnes, testicls, ovary and lesion skin, followed by the pancreas, brain, submandibular and mesenteric lymph nodes, whereas a low virus level was shown in the heart, spleen and liver. The primary target cells included respiratory tract epitheliocytes, macrophages, endotheliocytes, fibroblasts, plasmocytes, reticular, and smooth muscle cells [72,73]. MPXV was disseminated in marmots through the lymphogenic and hematogenic ways [72]. The ground squirrel can also be used to assess drug efficacy mpox [73], suggesting a potential animal model for mpox to develop therapeutic drugs and vaccine against MPXV.

Thirteen-lined ground squirrels (*Spermophilus tridecemlineatus*) intraperitoneally (i.p.) and i.n. infected with MPXV developed a fulminant illness, and all animals died 6–9 dpi [44]. Virus could be isolated in the blood and oropharynx. The major pathologic findings were seen in the liver that showed steatosis, centrilobular necrosis, and basophilic inclusion bodies in hepatocytes, and interstitial inflammation in the lung and splenic necrosis and were also observed [44].

The pathologic features of MPXV in ground squirrels are similar to those of macaque infection with MPXV and severe smallpox. Additionally, *S. tridecemlineatus* is abundant in grassland and has prairie habitats in the United States and Canada, whose adult weight of 140–252 g, cage requirement, and laboratory diet are similar to those of guinea pig and hamster. These factors make it possible to become an alternative animal model for MPXV.

6.3. Prairie dogs (*Cynomys ludovicianus*)

Exposure to MPXV-infected prairie dogs resulted in human infections in the United States [12,74,75]. Experimentally, prairie dogs can be infected with MPXV by intranasal, intradermal, and intraperitoneal routes, suggestive of a high susceptibility of the animal to the virus. The intraperitoneally infected prairie dogs all died 8–11 dpi, with the mains clinical symptoms of lethargy, inappetence, weight loss, nasal discharge, and lesion development. Significant hepatic and splenic necrosis was also observed, along with inflammatory changes in the lung [43]. Intranasal exposure to MPXV caused the primary pathologic changes in the pleural cavity and lung, with a mortality of 60%. Virus could be isolated from the nasal discharge and oropharynx. The ulcerative lesions were observed on the lips, tongue, and buccal mucosa of the infected animals, suggesting that MPXV can be transmitted by infected prairie dogs to susceptible animals by exposure to respiratory secretions, nasal mucous, contaminated bedding, or co-housing [43,76].

Importantly, prairie dogs exhibited a disease progression similar to the human MPXV, which included an asymptomatic period followed by a generalized rash progressing from macules to pustules. Prairie dogs may thus be a valuable surrogate model for MPXV infection [77]. This model has been used to evaluate vaccine and antiviral efficiencies against systemic MPXV infection [78,79].

Because the ground squirrels and the prairie dogs have a low fecundity rate, and a complex husbandry requirement, they must be obtained from their natural habitats, therefore having potential unknown pathogens. By comparison, the African dormouse can be easily propagated, with many characteristics similar to those laboratory mice; but they also have some disadvantage of few commercially available reagents and poorly understood biology.

7. Rabbit model

The susceptibility of rabbits to MPXV depends on the inoculation route and animal age. Intravenous inoculation of adult rabbits with 10^7 PFU of the classical strain Copenhagen resulted in a severe disease 3–7 dpi, including fever, rhinitis, conjunctivitis, extensive rashes on the mucous and skin membranes, and weight loss. The rashes occurred 5–6 days postinoculation, followed by the appearance of papules that developed into pustules [37]. The crusts usually began to form 8 dpi, and fell off after a fortnight. Eleven out of twelve rabbits survived the infection and one died of cachexia a month later. The virus could not only be isolated from the blood and tissues during the disease course, but also detected in the testicle tissues in some convalescent animals. The rabbits inoculated by the intravenous route developed antibodies 7 dpi, reached the peak by 14 days and persisted for more than 12 months. Virus neutralizing antibodies in a titre of 640 were also detected more than a year later. Young rabbits are more susceptible to intranasal inoculation than adult animals. The infected animals lost appetite and weight, but no rash was observed, with the disease terminating in death within 4–5 days [37].

Other routes of infection, including on scarified skin, intradermal, and oral inoculations are also capable of producing clinical symptoms. Rabbits infected on scarified skin (10^5 and 10^6 PFU) developed a localized papulopustular eruption at the inoculation site, and some animals had fever, rash on the skin, and mucous membranes [37]. Intradermal inoculation (10^5 and 10^6 PFU) produced dense infiltrates with necrosis and hemorrhages in the center [37]. However, no clinical sign occurred in adult rabbits by oral inoculation, even with a high dose (1.4×10^9 PFU) of the virus [37].

Young rabbits are shown to be much more susceptible to MPXV. The 10-day-old rabbits infected orally (10^6 and 10^7 PFU) developed an acute generalized process with rash, adynamia, appetite loss, and diarrhoea occurring 4–6 days after oral inoculation. Eruptions around the lips and nose and on the inner side of the ears were observed in most infected animals, with subsequent rash, suppurative conjunctivitis and rhinitis spreading over the body. The disease was accompanied by considerable loss of weight and as a rule ended in death 4–14 dpi. The virus could be isolated from blood, lung, liver, and spleen of a young rabbit at the acute stage of the disease. The infection was transmitted from infected rabbits to uninfected animals of the same litter, suggestive of contact or air-borne droplet transmission of MPXV [80].

8. Nonhuman primate model

Nonhuman primates (NHPs) are the most genetically related to humans, and the clinical diseases by both natural and experimental infection with MPXV have been described in several nonhuman primate species, including macaques and marmosets, showing that they can recapitulate the natural infection process of MPXV and are considered the ideal animal model for studying MPXV infection.

8.1. Macaques

Cynomogus macaques intramuscularly infected with MPXV caused a systemic clinical infection with widespread vesicular-pustular rash, but also developed a large area of skin and muscle necrosis [81]. Thus, nonhuman primate-MPXV models are usually developed through intravenous, aerosol and intratracheal infection routes [82]. Early studies reported rhesus macaques with intravenous inoculation of MPXV had a generalized vesiculopustular rash [83,84]. Recently, rhesus macaques received an intravenous dose of 2×10^7 PFU MPXV Zaire-79 developed a severe disease and eventually death 7–14 dpi [47]. Lesions in these animals included a disseminated vesiculopustular rash, marked lymphadenopathy up to 20 times normal size, mild splenomegaly, and pulmonary edema. Likewise, cynomolgus macaques infected with 5×10^7 PFU of MPXV Zaire-79 by the same inoculation produced a generalized vesiculopustular rash that began on the extremities and head, spreading to the whole body, like human MPXV [85]. Clinical presentations included fever, leukocytosis, lymphadenopathy, splenomegaly, and pulmonary edema [85]. Cynomolgus macaques usually displayed more severe clinical signs with more pronounced rashes [81]. Mechanically, natural killer (NK) cells massively proliferated upon MPXV infection. However, the migrating capacity of NK cells to peripheral tissues was significantly reduced, and the functions of cytokine secretion and cytotoxicity were largely compromised [86].

Aerosol inoculation is considered to be the principle respiratory model of MPXV infection, which is close to the natural transmission. However, it requires specialized facilities for aerosolization of pathogens, and it is difficult to assess the actual infection dose [87]. A direct delivery method may provide an easily measured infection dose. Intratracheal infection permits direct injection of a precise viral doses into the trachea, leading to development of a novel challenge technique by directly delivering an aerosol above the tracheal carina using a microsprayer attached to a bronchoscope with a high-pressure syringe [88].

The systematic pathological characterization of cynomogus macaques infected with aerosolized MPXV has been described [46,89]. Death of animals occurred 9–17 dpi, which was associated with fibrinonecrotic bronchopneumonia. Necrotizing lesions were seen in lymphoid organs, reproductive organs, and skin and mucosal surfaces, due to the systemic virus dissemination through the monocytic cell-associated viremia. Lower airway epithelium was the principal target of primary infection. Mandibular, mediastinal, and tonsil lymph nodes were also affected in the early infection course. The high viral titers were found in the lung tissues, and epithelial proliferation was seen in the mucosal skin and tissues, and intracytoplasmic inclusion bodies and multinucleated syncytial cells were occasionally observed in the epithelium of the tonsil, oral cavity, skin, and gastrointestinal tract. The distribution of lesions and development of vesiculopustular rash in these aerosol-challenged macaques resembled those of macaques infected with MPXV and humans MPX, with the exception of bronchopneumonia. Intranasal challenge with MPXV coursed lesions similar to those in the aerosolized model. The distinguishing feature of lethal infection by aerosolized MPXV in cynomolgus monkeys included the severe fibrinonecrotic bronchopneumonia, which has also been described for the fatal cases of human mpox [24].

Other infection routes in macaques, including aerosol, intrabronchial, and intratracheal infection, recapitulate

the essence of natural infection of MPXV, but still require a high virus dose and have the lesional burdens of infection route.

8.2. Marmosets (Callithrix jacchus)

Marmosets have become more common animal to model multiple viral diseases, including Ebola, Lassa fever, Eastern Equine Encephalitis, Marburg, Rift Valley Fever, Dengue, Hepatitis C, and influenza. Outbreaks of poxvirus in marmosets have been reported [90,91]. Animals were intravenously challenged with either 2.4×10^7, 9.5×10^5, 7.8×10^4, 5.0×10^3, 510, or 48 PFU MPXV Zaire-79. All animals showed a similar disease course, and finally died; animals at high dose succumbed relatively quickly, with generalized hemorrhagic manifestations, whereas animals at low dose survived longer, with more focal or discrete epidermal lesions. Marmosets produced a high viremia, and had similar pathological features with human mpox, such as hemorrhagic rash, and decrease in platelets [49].

In contrast, intranasal infection with 1,000 PFU MPXV was sufficient to recapitulate human MPXV infection in marmosets, including an incubation period of approximately 13 days, rash, viremia, and oral shedding, and death occcurred 15–17 dpi. Interestingly, female animals had more lesions (a greater number of lesions) and lower viral burden (viremia and oral shedding) than male, suggesting a possible gender effect [48].

Additionally, calpox virus infection in marmosets also caused disease progression and pathological findings similar to lethal orthopoxvirus infections in humans and in other NHPs [92]. Therefore, marmosets can be considered to be relevant to investigate the pathogenesis mechanisms and pathology of orthopoxvirus, including MPXV, and to evaluate their vaccines and antiviral therapies.

9. Application of animal models

9.1. Pathogenesis

Various animal models have provided an important platform to characterize MPXV infection and to compare pathogenesis between different isolates. The different pathogenicity between the CB and WA clades has been demonstrated by using the CAST/EiJ model. An intranasal challenge with 10^3 PFU, 87% of the MPXV-2003-044-infected animals survived as comparison with only 40% for MPXV Zaire-79. The high dose of 10^4 was 100% lethal for animals that were infected with MPXV Zaire-79, but only 50% lethal for animals that were infected with MPXV-USA. Likewise, MPXV Zaire-79 and MPXV-2003-044 could cause weight loss of 22.4%–26.4% and 10.5%–18.1%, respectively [36]. A recently emerged Canadian MPXV isolate SP2833 did not cause any disease in CAST/EiJ mice through intranasal route at a dose of 2×10^4 PFU, with mean weigh gain of 10%–20%; a high dose of 10^6 PFU of SP2833 only experienced some weight loss of less than 10% [33]. The CAST/EiJ mice is thus very useful to identify the virulence factor for MPXV [93].

Inbred mice are considered to be ideal small animal models for infectious diseases; however, common mouse strains are relatively resistant to MPXV infection. However, the *stat1*$^{-/-}$, SCID, and suckling mice, and some wild inbred mice, such as CAST/EiJ, PERA/EiJ, and MOLF/EiJ are shown to be susceptible to MPXV infection [94]. Understanding the molecular basis of the susceptibility of these mice may contribute to elucidating of virus pathogenicity and host defense mechanisms, and to explaining the possible effectiveness of this mouse strain as a model system for antiviral drug and vaccine evaluation. Different susceptibility of these animals provides a chance to determine host factors associated with MPXV infection. For example, comparison studies have demonstrated that insufficient innate immunity is associated with the susceptibility of these animals, and IFN-γ plays an importance role to protect against MPXV disease [39,95]. The inherent susceptibility of CAST mice to orthopoxvirus is associated with the low level of natural killer (NK) cells, and IL-15 can enhance NK cell numbers, thereby protecting against lethal infection with orthopoxviruses [96]. In contrast, BALB/c mice have a greater production of IFN-γ than CAST mice [39,70]. In addition, IFN-γ and its receptor-knockout C57BL/6 mice are more susceptible to MPXV infection than parental C57BL/6 mice; exogenous IFN-γ can protect CAST mice against MPXV infection [39]. STAT1 can up-regulate host response through types I, II, or III IFN signaling, while STAT1-deficient mice are more susceptible to MPXV infection than IFN-γ- and IFN-γ receptor-deficient mice [40].

9.2. Vaccine evaluation

Animal models have widely been used to evaluate immunogenicity and protective efficacy of candidate vaccines against MPXV infection and diseases. In these studies, survival was the primary end point. Modified vaccinia virus Ankara (MVA) was produced by continuous passages of vaccinia virus in chick embryo fibroblasts, resulting to multiple deletions and mutations and inability to replicate efficiently in humans. Cynomolgus monkeys (*Macaca fascicularis*) immunized with MVA twice (months 0 and 2/4) produced virus-specific neutralizing antibody and T cell responses, and completely protected against a lethal infection with MPXV by both intravenous and intratracheal challenge [97,98], and a single dose of MVA could induce rapid protective immunity at 6 days after immunization [99]. LC16m8 is another highly attenuated smallpox vaccine in Japan, which was developed through multiple passages of the smallpox vaccine Lister strain in

rabbit kidney cells, and a single dose of LC16m8 can provide protection in cynomolgus monkeys against s.c. challenge with 10^6 PFU MPXV Zr-599 for longer than one year [100].

MVA is also a popular vaccine vector for the expression of recombinant proteins, whose clinical effects have been assessed in NHP models. For example, MVA expressing 5 genes of simian human immunodeficiency virus (SHIV)/89.6P provided durable protection against SHIV and MPXV in rhesus macaques [101]. The integration of IL-15 cytokine into the genome of vaccinia strain Wyeth (Wyeth/IL-15) conferred long term protection against a lethal challenge in cynomolgus monkeys [102]. In another study, a subunit vaccine prepared from the soluble fractions of MPXV mechanically disrupted by low temperature and high pressure could elicited virus-neutralizing antibody responses and completely protected against s.c. challenge with $8 \times 10^{4.6}$ PFU MPXV strain Copenhagen in rhesus macaques [103]. A DNA vaccine with 4 vaccinia virus genes of L1R, A27L, A33R, and B5R induced protection from severe disease after a lethal challenge, whereas rhesus macaques vaccinated with a single gene of L1R encoding a target of neutralizing antibodies showed severe clinical disease, but all animals survived [47].

Alphavirus replicon vectors of Venezuelan equine encephalitis virus are being used to develop alternative to the current vaccine against smallpox, whose recombinant expressing the vaccinia virus A33R, B5R, A27L, and L1R genes induced protective immune responses in mice, and the immunized cynomolgus macaques survived i.v. challenge with 5×10^6 PFU MPXV Zaire-79 strain [104]. The New York City Board of Health (NYCBH) vaccinia virus is used in the US to protect against smallpox, and the attenuated strain, in which the E3L gene (NYCBH E3L) involved in innate immune evasion has been deleted, confered partial protection (75%) against lethal MPXV infection in cynomolgus macaques [105].

Dryvax is a live cowpoxvirus-based vaccine and can induce long-lasting cross- immune protection against variola and other poxviruses. Dryvax-immunized Rhesus macaques and Chimpanzees had protective effects against MPXV challenge, with no visible clinical signs and skin lesions seen on the vaccinated animals [106].

In China, the vaccinia virus Tiantan strain served as a smallpox vaccine [107], and immunization of mice could produce antibodies cross-reactive with protective antigens of MPXV [108]. Further investigation should be conducted to determine the protective effect of the vaccine against MPXV challenge.

9.3. Drug evaluation

In addition to vaccine-based immune protective effects, animal models are also use to assess small molecules for antiviral activity. Tecovirimat (ST-246), an inhibitor of the VP37 envelope wrapping protein in orthopoxvirus, is approval for the treatment of smallpox. Tecovirimat shows broad-spectrum antiviral activity against orthopoxviruses, and can protect lethal MPXV challenge in NHP and rodent models [85]. ST-246 at an oral dose of 10 mg/kg/d for 14 days starting at 3 dpi not only protected from death, but also significantly reduced the lesions and viremia levels in cynomolgus monkeys [109,110]. Treatment with ST-246 initiated up to 8 dpi increased survival, while it initiated up to 4 dpi protected animals from severity of clinical manifestations [111]. In cynomolgus macaques, oral ST-246 as late as 7 dpi significantly improved survival in the lethal aerosol challenge, while earlier treatment (before 5 dpi) significantly reduced the severity of diseases, such as clinical signs, weight loss, and viremia [112,113]. In the STAT1-deficient C57BL/6 mice i.n. infected with 5,000 PFU of MPXV ZAIRE-79, mice treated with daily 100 mg/kg of ST-246 for 10 days survived the infection and had no significant weight loss [40]. Additionally, daily oral daily ST-246 also markedly reduced viral titers in the tissues in CAST/EiJ mice infected with the MPXV strain isolated in the current outbreak [33]. However, coadministration of ST-246 and a live attenuated smallpox vaccine (ACAM2000) in cynomolgus macaques can reduce the vaccine-induced humoral responses, suggesting how vaccine and tecovirimat are clinically used [112].

Cidofovir is a viral DNA polymerase inhibitor that also has antiviral effects on lethal MPXV infection in cynomolgus macaques. Monkeys were inoculated intratracheally with 10^7 PFU of MPXV CB strain, and i.p. administered 5 mg/kg cidofovir 1, 3, 7, 10, and 13 dpi, or 1, 3, 5, 7, 10, and 13 dpi, respectively. Animals treated with cidofovir were protected from severe disease and death, and had significantly lower viremia than the control animals, and MPXV-specific plasma IgG antibodies developed at 13 dpi [114]. Additionally, cidofovir could reduce the immune responses elicited by the smallpox vaccine Dryvax when co-administration of cidofovir, however, cidofovir can reduce the side effects of vaccine [115].

Other animals, such as ICR mice and ground squirrels (*Marmota bobak*), prairie dogs, were also used to assess antiviral effects of ST-246 and NIOCH-14, a derivative of tricyclodicarboxylic acid, showing similar results to those reported in NHP models [53,73,78]. Importantly, ST-246 could treat systemic MPXV infection in prairie dogs, in which animals were intranasally challenged with 65 LD_{50}, and administered ST-246 for 14 days, beginning on 0 and 3 dpi, or after the onset of rash. All animals that received treatment of ST-246 survived, and animals that received treatment before symptom onset were largely asymptomatic. Virus DNA was undetected or at greatly a low level in animals received treatment on 0 or 3 dpi, compared to the control animals or animals treated after rash onset. All the animals treated after rash onset recovered [78].

10. Conclusions

Currently, there are no MPXV-specific vaccines and antiviral drugs available. Development of animal models of MPXV is essential to investigate medical countermeasures, including a detailed characterization of the pathogenesis and lesions in susceptible hosts. Although the characterization has been investigated in some animal models, most of them are derived from MPXV historic isolates (Table 3). Thus, further investigation is clearly needed to identify pathogenesis of circulating MPXV strains.

NHPs have immunological and anatomical features similar to humans, thus are usually considered as the fundamental animal models of MPXV and other emerging pathogens. However, NHPs are relatively expensive, including purchase, housing, infection, sampling, and tissue analysis, and pregnant animals are more expensive. limiting the number of used animals that affects the statistical analysis. Moreover, under biocontainment conditions, the issues of housing and handling are particularly significant, as there is limited space, and personnel must wear special protective equipment, making it is difficult to complete the simplest experiments.

Rodents and rabbits are much less expensive, as they require less housing space, and are easier to handle than NHPs. Additionally, most of the commercially available animals provide the opportunity to conduct some researches that require well-characterized and relatively uniform animal populations. The primary disadvantages of rodents and rabbits are their immunologic and anatomic differences from humans. Moreover, the small body size of these animals limits the blood volume and other samples of single animal as comparison with that of NHPs. Several wild rodents, such as the ground squirrels, prairie dogs, and African dormouse, are highly susceptible to MPXV. However, these animals are difficult to propagate, as they have complex husbandry requirements, and have low fecundity rates, and, and there are few commercially available reagents.

No one animal model can recapitulate all clinical aspects of human MPXV infection, and the features of the multiple animal models should be integrated to provide a more complete profile of the disease. Although great progress has been made, the refinement and use of these animal models will result to greater knowledges of many remaining scientific questions, including (i) pathogenicity and pathological characteristics of the current 2022 MPXV strains in various animal models, (ii) the mechanism of MPXV persistence in the reproductive system, nervous system or other tissues, (iii) sexual and maternal-infant transmission modes of MPXV, (iv) the immune mechanisms involved in MPXV clearance and protection, (v) the roles of virus variation and sequence polymorphisms in MPXV pathogenesis, (vi) evaluation of therapeutic and preventive effects of potential drugs and vaccine against the current 2022 MPXV strains, (vii) the molecular basis of viral cellular tropisms, (viii) the viral and host factors that facilitate infection, (ix) the transmission capacity of different MPXV strains, and (x) the possibility of asymptomatic infected individual to transmit MPXV.

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Declaration of competing interest

The authors declare no completing interests.

Data available statement

No data, models, or code were generated or used during the study.

Ethics statement

An ethical statement is not required as there were no human subjects involved in this study.

Informed consent

Not applicable.

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