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Research Progress on Animal Models of Monkeypox Virus Infection and the Application in Vaccine Quality Evaluation

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ABSTRACT

Monkeypox is a zoonotic disease caused by the Monkeypox virus, a member of the genus *Orthopoxvirus* within the family *Poxviridae*, currently classified into the West African clade and Congo Basin clade. Existing studies have primarily utilized mice (e.g., CAST/EiJ, BALB/c), rabbits, and non-human primates (e.g., rhesus monkeys, marmosets) as infection models. However, these models still have limitations in accurately simulating human disease characteristics and immune responses. In addition, vaccine evaluation systems for various MPXV strains have not been fully established, and relevant studies remain insufficient. This paper reviews the progress of animal models infected with MPXV and their application in vaccine evaluation, aiming to provide references for optimizing model selection and enhancing vaccine development strategies.

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Abbreviations: MPXV, Monkeypox Virus; VACV,Vaccinia Virus; MVA, Modified Vaccinia Ankara; IMV,Intracellular Mature Virion; IEV, Intracellular Enveloped Virion; CEV, Cell-associated Enveloped Virion; EEV, Extracellular Enveloped Virion.

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Introduction

The Monkeypox virus (MPXV) was first identified in 1958, with the first human case reported in 1970 in a male infant in the Democratic Republic of Congo, followed by a gradual increase in infections across Africa. MPXV transmission occurs among animals (primarily primates and rodents), between animals and humans, and through human-to-human contact[1]. In recent decades, MPXV infections were predominantly confined to Africa; however, globalization and population mobility facilitated its spread. By 2022, a global monkeypox outbreak impacted 110 countries and territories, with the World Health Organization (WHO) reporting 1,423 confirmed MPXV cases across 31 non-endemic nations and zero fatalities[2]. Consequently, WHO declared the outbreak a Public Health Emergency of International Concern (PHEIC) in July 2022. The predominant circulating strain during this period was clade IIb, characterized by relatively low case fatality rates and transmission primarily among men who have sex with men (MSM). Subsequent WHO risk assessments classified the global threat as moderate, with moderate risk in the African, Eastern Mediterranean, European, and Americas regions, and low risk in Southeast Asia and Western Pacific regions. Accordingly, WHO de-escalated the PHEIC designation in May 2023. Between 2022 and 2023, global MPXV case reports declined significantly. However, a resurgence in Africa involving clade Ib (a sublineage of clade I) has recently emerged, distinct from prior outbreaks. This variant exhibits increased infectivity in children and higher mortality rates. Epidemiological data indicate a case fatality rate of 0.2% during the 2022 outbreak, compared to approximately 3% in the current outbreak, highlighting its increased severity. On August 14, 2024, WHO reinstated the PHEIC designation in response to the escalating outbreak in Africa.

Vaccination, as a simple, safe, and effective strategy, remains critical to curbing monkeypox transmission. MPXV vaccines are categorized into four generations: First-generation smallpox vaccines confer cross-protection against MPXV; second-generation live Vaccinia virus (VACV) vaccines (ACAM2000) induce VACV-specific CD4+ and CD8+ T-cell responses persisting at 1, 3, 6, and 12 months post-vaccination; third-generation attenuated vaccines, such as Modified Vaccinia Ankara (MVA)-based JYNNEOS, exhibit improved safety profiles compared to earlier generations[3]. However, JYNNEOS requires two doses administered 28 days apart, rendering the second dose potentially ineffective for post-exposure prophylaxis, with uncertain therapeutic efficacy from a single dose. Fourth-generation vaccines, including MPXV-specific recombinant protein

vaccines and RNA-based platforms (mRNA and circular RNA), utilize MPXV-derived antigens rather than orthopoxvirus homologs. To date, no MPXV vaccines have been approved in China, though multiple biopharmaceutical entities and research institutes are developing replication-defective monkeypox attenuated live vaccines and mRNA-based candidates. On September 9, 2024, the Shanghai Institute of Biological Products (China National Biotec Group) announced regulatory approval for clinical trials of its self-developed MVA-based monkeypox attenuated live vaccine, marking China's first MPXV vaccine candidate to enter clinical evaluation.

Animal models are indispensable in vaccine development for elucidating disease pathophysiology and therapeutic mechanisms across species[4]. Current epidemiologic-pathologic paradigms, such as those for COVID-19, leverage primate, rodent, and porcine models to identify infection dynamics and therapeutic strategies. Robust vaccine evaluation relies on animal models that recapitulate human infection processes and pathological features, enabling systematic investigations into disease mechanisms and therapeutic efficacy[5].

This review synthesizes advances in MPXV-infected animal models and their applications in vaccine evaluation, aiming to inform novel model development and accelerate MPXV vaccine research.

Brief description of MPXV

1. Morphology and genome of MPXV

The MPXV, a member of the genus orthopoxvirus within the family poxviridae, exhibits a brick-shaped or oval morphology with a diameter of approximately 200–250 nm[6,7]. Its nucleocapsid displays a dumbbell-like structure enclosed within an ovoid lipid-containing particle[7]. The MPXV genome consists of a linear double-stranded DNA approximately 197 kb in length, encoding ~180 proteins[1,8]. Genomic organization includes a central conserved region flanked by two variable regions and two terminal inverted repeats. The high genomic homology (>90%) between MPXV and other orthopoxviruses primarily resides in the central conserved region[1,9]. Most proteins encoded by the MPXV genome share functional similarities with their orthopoxvirus homologs[10]. For instance, MPXV genes M1R, A29L, A35R, and B6R exhibit >95% sequence homology with Vaccinia virus (VACV) genes L1R, A27L, A33R, and B5R, respectively, encoding proteins with analogous functions.

The replication cycle of poxviruses typically initiates within 2~5 hours post--infection, with viral maturation progressing through five distinct stages: immature virion (IV), intracellular mature virion (IMV),

intracellular enveloped virion (IEV), cell-associated enveloped virion (CEV), and extracellular enveloped virion (EEV), culminating in a ~6-hour replication cycle[11]. IMV and EEV represent the primary infectious forms, with EEV demonstrating enhanced infectivity via pH-independent membrane fusion for cellular entry. The MPXV A35R gene product is critical for intercellular viral dissemination. EEV mediates cell-to-cell transmission, while IMV, released into the extracellular environment, ensures interhost transmission due to its superior stability [12].

2. Pathogenesis and Symptoms

The pathogenic mechanism of MPXV resembles that of VACV, requiring no specific host receptors or molecules for cellular entry and replication, enabling broad infectivity across mammalian cells[13]. During initial infection, EEV interact with primary attachment receptors (glyco--saminoglycans) on host cell membranes via MPXV surface proteins, facilitating cellular entry[14]. Following membrane fusion of EEV or IMV, viral core components are released into the host cytoplasm[15]. MPXV exclusively replicates its nucleic acids in the

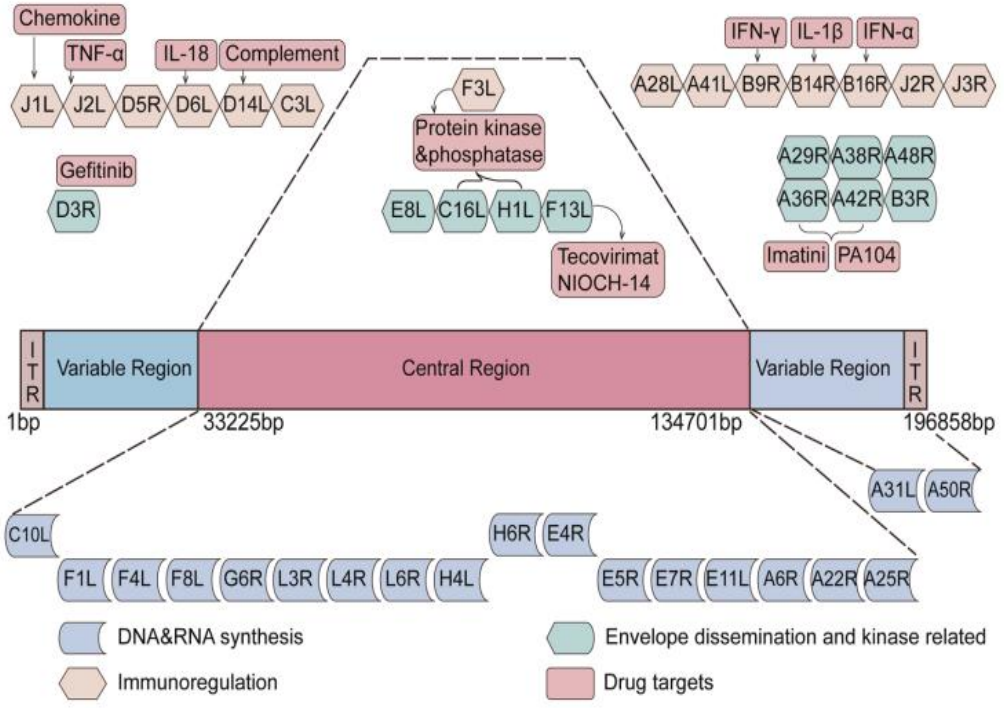

Figure . Genomic structure and potential antiviral targets of MPXV [1]

cytoplasm, encoding proteins that facilitate genome replication and transcriptional regulation[16]. The precise mechanisms underlying viral-cell membrane interactions remain incompletely characterized. A17L--specific antibodies restrict viral entry, while L1R-a myristoylated transmembrane protein (250 residues essential for virion maturation)-serves as another target for neutralizing antibodies[17].

The incubation period for MPXV infection ranges from 6~13 days, with common symptoms including fever, headache, and myalgia[18]. Lesions typically progress through four stages: macules, papules, vesicles, and pustules, culminating in scab formation and desquamation[19]. Early infection often manifests as oral ulcers and cutaneous eruptions characterized by firm, spherical rashes (0.5~1 cm diameter) accompanied by pruritus and pain[20]. Within two weeks, rashes evolve sequentially from maculopapular to vesiculopustular stages, followed by scab shedding over subsequent weeks. Residual erythema, hyperpigmentation, or scarring may persist for years. While most patients recover within weeks, severe cases may progress to fatal outcomes.

Unvaccinated patients exhibit higher case fatality rates, more extensive rashes, and exacerbated clinical severity[21]. Epidemiologic patterns correlate with disease severity, as African cases demonstrate clinical parallels to but greater severity than those in non-endemic regions (e.g., the United States)[22]. At the August 2024 WHO World Conference on Monkeypox Vaccines and Innovations, data highlighted the escalating African outbreak driven by divergent MPXV clades and underscored the urgent need for vaccine production in regions with limited healthcare infrastructure.

Progress on the animal models of MPXV infection

1.Hosts of MPXV

While the natural reservoir host of MPXV remains unidentified, African rodents are strongly implicated in its transmission[23]. Numerous African animals, including tree squirrels (Funisciurus spp.), Gambian pouched rats (Cricetomys gambianus), rope squirrels (Funisciurus spp.), dormice (Graphiurus spp.), and non-human primates, are susceptible to MPXV infection. Consumption of undercooked meat or animal products from infected animals poses a significant risk factor[24].

2.Experimental animal models of MPXV infection

2.1 Mice

Mice are widely utilized in vaccine and therapeutic research due to their ease of husbandry, high reproductive rates, and well-characterized immune systems. Most mouse strains exhibit no clinical signs post-MPXV infection. Among wild-type

mice, only CAST/EiJ, MOLF/EiJ, and PERA/EiJ inbred strains demonstrate susceptibility, with CAST/EiJ mice showing dose-dependent responses: 10^2 PFU induces mild clinical symptoms and weight loss, while 10^4 PFU results in 100% mortality, particularly via intraperitoneal inoculation[25, 26]. Intranasal cytokine administration in CAST/EiJ mice confers protection against MPXV, implicating insufficient interferon-γ responses in pathogenesis[27]. Advantages of CAST/EiJ models include high MPXV sensitivity, genetic homogeneity, commercial availability, and compatibility with immunological assays, making them valuable for studying pathogenesis and evaluating vaccines/therapeutics[28].

BALB/c and C57BL/6 inbred strains are employed to compare MPXV clade virulence, revealing subtle pathogenicity differences between strains[29]. Subcutaneous or intranasal inoculation in these strains elicits greater edema in BALB/c versus C57BL/6 mice. While neither model fully recapitulates human MPXV disease, they remain instrumental in mechanistic studies, virulence assessments, and preliminary vaccine/drug testing.

2.2 Rabbits

Rabbits are favored for their rapid skeletal maturation, low cost, hardiness, and ease of handling. Susceptibility to MPXV depends on inoculation route and age. Intravenous administration of 10^7 PFU MPXV in adult rabbits induces fever, weight loss, and cutaneous lesions[30]. Juvenile rabbits (10-day-old) infected with 10^6~10^7 PFU develop acute generalized rash, lethargy, anorexia, and diarrhea within 4–6 days[31].

New Zealand White (NZW) rabbits exhibit distinct phenotypic responses based on inoculation routes. Intradermal MPXV injection at varying titers produces dose-dependent lesion sizes on dorsal skin, peaking at 7~9 days post-infection (dpi) and resolving by ~11 dpi. However, low viral titers fail to elicit significant lesion differentiation, necessitating high-dose challenges. Intravenous high-titer MPXV administration induces dorsal lesions and detectable viral loads in organs (e.g., lungs), supporting NZW rabbits as potential models for MPXV tropism and therapeutic studies.

2.3 Non-human primates (NHPs)

Rhesus macaques (Macaca mulatta) develop a systemic infection characterized by a disseminated vesiculopustular rash and extensive dermal and muscular necrosis following intramuscular inoculation with monkeypox virus (MPXV)[32]. Intravenous administration of 10^7 PFU MPXV in rhesus macaques causes generalized pustular rash, lymphadenopathy, and 100% mortality within 7~14 days[33].Cynomolgus macaques (Macaca fascicularis) exhibit similar yet more severe symptoms, including fever, enlargement of immune organs, and a

centrifugal rash that progresses from the extremities, closely mimicking human MPXV infection[34].

Marmosets (Callithrix jacchus) infected intravenously with MPXV (10^3~10^7 PFU) display dose-dependent lethality: higher doses induce hemorrhagic manifestations and extensive cutaneous lesions, while lower doses prolong survival with attenuated symptoms[35]. Their clinical parallels to human MPXV infection (e.g., pox lesions) position marmosets as robust models for orthopoxvirus pathogenesis studies and therapeutic evaluations[36].

Progress of experimental animal models for evaluation of monkeypox and related vaccines

Although animal models for MPXV infection in humans are rare, laboratory animal models are frequently used in quality evaluation of monkeypox vaccines and related vaccines, such as smallpox vaccine, summarized below.

1. Rhesus monkey

Rhesus monkeys were used as an animal model to compare the immunogenicity and protective effects of ACAM2000, MVA and vector subunit vaccines on MPXV[37,38].The three vaccines provided strong protection after high-dose intravenous MPXV challenge against the current outbreak strain, with ACAM2000 providing near-complete protection and JYNNEOS and Ad35 vaccines providing strong but incomplete protection[39]. A stronger correlation between neutralizing and binding antibody titers and protection than T cell responses was observed in the rhesus monkey model [37].

2. BALB/c mice

BALB/c mice were employed to evaluate the protective efficacy of mRNA vaccines encoding MPXV antigen fusion proteins against VACV[37]. In this study, three mRNA vaccines were designed: two encoding fusion proteins of MPXV A35R extracellular domain and M1R (VGPox 1 and VGPox 2), and one comprising a mixture of full-length A35R and M1R mRNAs (VGPox 3)[38]. All three vaccines induced early anti-A35R antibodies in female BALB/c mice, but only VGPox 1 and VGPox 2 generated detectable anti-M1R antibodies by day 7 post--vaccination. All mRNA vaccine groups conferred complete protection against lethal VACV challenge[37]. BALB/c mice were also used to assess a bivalent fusion vaccine combining MPXV extracellular enveloped virion antigen A35 and intracellular mature virion antigen M1 (termed DAM)[38]. Compared to co-administration strategies, DAM preserved native epitope conforma--tions of both antigens, eliciting stronger A35- and M1-specific antibody responses and enhanced in vivo protection against VACV[38]. Aluminum-adjuvanted DAM demonstrated safety and robust protection against lethal VACV challenge, with

pilot-scale production confirming high yield and purity[38].

Beyond subunit vaccines, MPXV circular RNA (circRNA) vaccines were evaluated in BALB/c mice[39]. Using a scalable circRNA platform, four circRNA vaccines expressing distinct MPXV surface proteins (A29L, M1R, A35R, B6R) induced potent neutralizing antibodies and T-cell responses, achieving effective VACV protection in BALB/c mice[39]. A tetravalent combination of these circRNAs provided optimal protection against VACV challenge[39]. Additionally, multivalent MPXV mRNA vaccines were tested in BALB/c models[40]. Two bivalent (LBA [B6R-A29L] and LAM [A35R-M1R]) and one tetravalent (LBAAM [B6R-A35R-A29L-M1R]) mRNA vaccines were evaluated for immunogenicity and protective efficacy in lethal challenge models[40]. All candidates elicited robust antigen-specific humoral and cellular immunity, with combined bivalent and tetravalent regimens outperforming individual bivalent vaccines in protection[40].

This study summarizes key animal models for vaccine evaluation in Table.

Discussion

How to deal with a new round of monkeypox epidemic challenges become a new hot spot. MPXV has a long incubation period in patients after infection, and its early symptoms are similar to those of influenza, so it is difficult to detect the virus when patients enter other countries. That is, overseas monkeypox virus carriers cannot be completely isolated and prevented from spreading to our country, so the development of vaccines against MPXV is very important. Although current data show that the vast majority of monkeypox transmission routes are through long-term close contact, such as sexual behavior, skin contact, and close breathing or conversation with others, and the ability to transmit from person to person is relatively weak, unlike the first wave of monkeypox two years ago. Unlike the epidemic, the most affected people this time are women and children under the age of 15. Children account for more than 70% of cases and 85% of deaths, and the mortality rate among children is four times that of adults. Therefore, the monkeypox epidemic is still something we cannot ignore and needs to pay attention to.

This study mainly reviews the animal models that have the potential to become MPXV and the animal models that have been applied and evaluated in MPXV vaccine design. It is necessary to establish human MPXV infected animals, which can deepen the understanding of the MPXV virus and promote the development of drug design and vaccine research.

Competing interests

The authors declare all financial and non-financial competing interests.

Table. Animal models in vaccine quality evaluation

Animal model	Function	Evaluation index	Evaluation results
Rhesus monkey	Comparison of ACAM2000, MVA and vector subunit vaccines	Humoral immunity (conjugated antibodies, neutralizing antibodies), cellular immunity (CD^{8+}, CD^{4+}T cells), in vivo tissue viral load	ACAM2000 provides near complete protection, and JYNNEOS and Ad35 vaccines provide strong but incomplete protection
Balb/c	Evaluation of the protective effect of mRNA vaccines containing monkeypox antigen fusion protein on VACV	Humoral immunity (A35R, M1R-specific antibodies, neutralizing antibodies), protective effect of VACV challenge (body weight, survival rate)	All three mRNA vaccines fully protected mice from VACV challenge
	To evaluate the immune and protective effects of DAM (bivalent fusion of A35 and M1)	Humoral immunity (A35R, M1R, DAM-specific antibodies, neutralizing antibodies), VACV challenge protective effect (body weight, survival rate, lung tissue virus titer)	DAM vaccine protects mice from deadly VACV attack
	Evaluation of the immune and protective effects of circular RNA vaccines	Humoral immunity (A35R, M1R, A29L, B6R-specific antibodies, neutralizing antibodies), cellular immunity (CD^{8+}, CD^{4+}T cells), VACV challenge protective effect (body weight, survival rate, viral load in lungs, turbinates and trachea, lung tissue changes)	Combination of four circular RNA vaccines shows optimal protection against VACV attack
	Evaluation of immune and protective effects of multivalent mRNA vaccines	Humoral immunity (A35R, M1R, A29L, B6R-specific antibodies, neutralizing antibodies), cellular immunity (CD^{8+}, CD^{4+}T cells), VACV challenge protective effect (body weight, survival rate, lung homogenate, turbinate virus genome copy number and VTT titer, lung tissue changes)	All mRNA vaccine candidates provide protection against VACV infection. The combined use of two bivalent mRNA vaccines and a tetravalent vaccine has better protective effects than the use of bivalent mRNA vaccine alone.
New Zealand rabbit	Evaluation of the protective effect of recombinant VACV vaccine on MPXV	Humoral and cellular immune response, number of spots, body temperature changes,histological scores of lungs and testicles	Induces a strong humoral and cellular immune response, and reduces the number of acne spots produced in the skin and organs, reduces the degree of pathological damage in the lungs and testicles, and reduces the titer of MPXV in organs.

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