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Review Article

Monkeypox: An outbreak of a rare viral disease

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Abstract Monkeypox is a viral zoonotic disease rarely found outside Africa. Monkeypox can be spread from person to person through close contact with an infected person, and the rate of transmission is not very high. In addition, monkeypox and variola virus are both pox viruses, and the spread of monkeypox virus was also controlled to some extent by the smallpox campaign, so monkeypox was not widely paid attention to. However, as smallpox vaccination is phased out in various countries or regions, people's resistance to orthopoxviruses is decreasing, especially among people who have not been vaccinated against smallpox. This has led to a significant increase in the frequency and geographical distribution of human monkeypox cases in recent years, and the monkeypox virus has become the orthopoxvirus that poses the greatest threat to public health. Since the last large-scale monkeypox infection was detected in 2022, the number of countries or territories affected has exceeded 100. Many confirmed and suspected cases of monkeypox have been found in individuals who have not travelled to affected areas, and the route of infection is not obvious, making this outbreak of monkeypox a cause for concern globally. The purpose of this systematic review is to further understand the pathophysiological and epidemiological characteristics of monkeypox, as well as existing prevention and treatment methods, with a view to providing evidence for the control of monkeypox.

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Introduction

The discovery of monkeypox

In 1958, an outbreak of an unidentified disease characterized by blisters on the skin occurred in a group of monkeys in Africa. A new virus was analyzed from the body of the infected monkeys and hence named monkeypox virus.[1] Monkeypox virus is a deoxyribonucleic acid (DNA) virus of the orthopoxvirus genus in the poxviridae family and is a viral zoonotic disease. Subsequent studies have found that monkeypox virus has a wide host range, including monkeys, squirrels, prairie dogs, and Gambian mice. Based on the indiscriminate nature of the virus, researchers speculated that the main natural host of monkeypox virus may be rodents.[2]

In 1970, the world's first documented case of a human infected with the monkeypox virus was diagnosed in a 9-year-old child in the Democratic Republic of Congo who developed symptoms similar to smallpox.[3] After the smallpox vaccine led to the eradication of smallpox virus, and since different orthopoxviruses had similar genetic and antigenic properties as smallpox, infection with any orthopoxvirus could lead to the production antibodies that may resist other orthopoxviruses.[4] Therefore, human infection with monkeypox virus was considered a rare, self-limited disease that received little attention. However, since the gradual cessation of smallpox vaccination in various countries, the population's resistance to various orthopoxviruses has been diminished over time. This has resulted in a significant increase in the frequency and geographical distribution of human monkeypox cases in recent years, and monkeypox virus has become the orthopoxvirus that poses the highest threat to public health.[5]

Pathophysiology of monkeypox

Monkeypox virus is an enveloped double-stranded DNA virus with similar morphological characteristics to members of the orthopoxvirus family. The genomes of monkeypox virus includes a central conserved region as well as reverse terminal repeats with tandem repeats, but virus-host interaction genes are relatively unconserved and localized in the terminal portion. Monkeypox virus exists in two forms: intracellular mature virus and extracellular envelope virus.[4] Monkeypox viruses can enter cells by attaching and fusing. After the monkeypox virus fuses with the host cell membrane, the mature virus is released from the infected cell through lysis, while the enveloped virus leaves the host cell through exocytosis. In other words, viruses transmit from cell to cell by attaching particles to the cell surface, while infected cells transmit throughout the body by releasing virions.

The clinical presentation of monkeypox is similar to that of the smallpox virus. The incubation period after infection with monkeypox virus is approximately three to twenty days, after which the patient begins to develop a series of rash symptoms lasting approximately two to five weeks.[6] There is not one specific symptom of monkeypox that indicated the start of the disease. Patients usually have fever, headache, lethargy, swollen lymph nodes, weakness, and muscle pain.[7] Within one to five days of the onset of fever, a rash of varying sizes begins to appear on the face, which then spreads to the trunk, hands, feet and gradually throughout the body. The rash goes through several stages of development (from macules to papules to blister to pustules) and gradually crusts over. However, these different stages of the rash may appear concurrently during the onset of symptoms. In addition, a monkeypox virus infection may result in organ damage leading to eye lesions, bronchopneumonia, skin lesions and, in rare cases, sepsis.[4] Refer to Fig. 1 for a depiction of the progression viral infection.

Epidemiology of monkeypox

Since the first human case of monkeypox was found in Congo in 1970, the majority of cases have been reported in Congo, Central Africa, and Nigeria.[8] It was not until 2003 that monkeypox was identified in the United States, the first case outside of Africa.[9] Since 2018, monkeypox has been detected in travelers from numerous countries including Nigeria, Israel, the United Kingdom, and Singapore.[10] Congo reported more than 4000 cases of monkeypox in humans in 2020 and more than 3000 cases in 2021.[11] Cases were previously reported mainly in Africa, but monkeypox cases have recently been reported in many countries, and in many areas, for the first time.[12] Since July 2022, monkeypox has re-emerged on a large scale and has been classified as a public health emergency until September, when the first imported case of monkeypox was reported in Hong Kong, China. Since 2023, patients infected with monkeypox have also been reported in Asia, including Japan and Taiwan.[13] In April 2023, monkeypox cases were reported in South Korea, and the number of patients infected with monkeypox continued to increase. It is important to note that a number of people infected with monkeypox have no history of travel to countries where monkeypox is endemic.

The known transmission modes of monkeypox virus include animal to human and human to human transmission as detailed in Fig. 2. Primary animal-to-human disease occurs when humans come into contact with the blood, bodily fluids, skin or mucous membrane of an infected animal, or are scratched or bitten by an infected animal.[14] Eating improperly cooked infected animals is also a risk factor.[15] Human-to-human transmission occurs when humans come into contact with the blood, bodily fluids, and contaminated materials of infected persons, which includes respiratory droplets.[16] In addition, monkeypox virus can be transmitted through sex.[17] Recent studies have shown that monkeypox, unlike mutable RNA viruses such as HIV or SARS-CoV-2, has a much more complex epidemiology than other viruses.[18] It is reported that the genome of the monkeypox virus in the new outbreak differs by about 50 nucleotide sites from that of the common monkeypox virus in Africa, and the mutation rate is greatly increased, resulting in the gene evolution and deletion of the monkeypox virus in the human-to-human transmission of the outbreak. These can be destabilizing factors that may change the epidemiology of monkeypox virus.

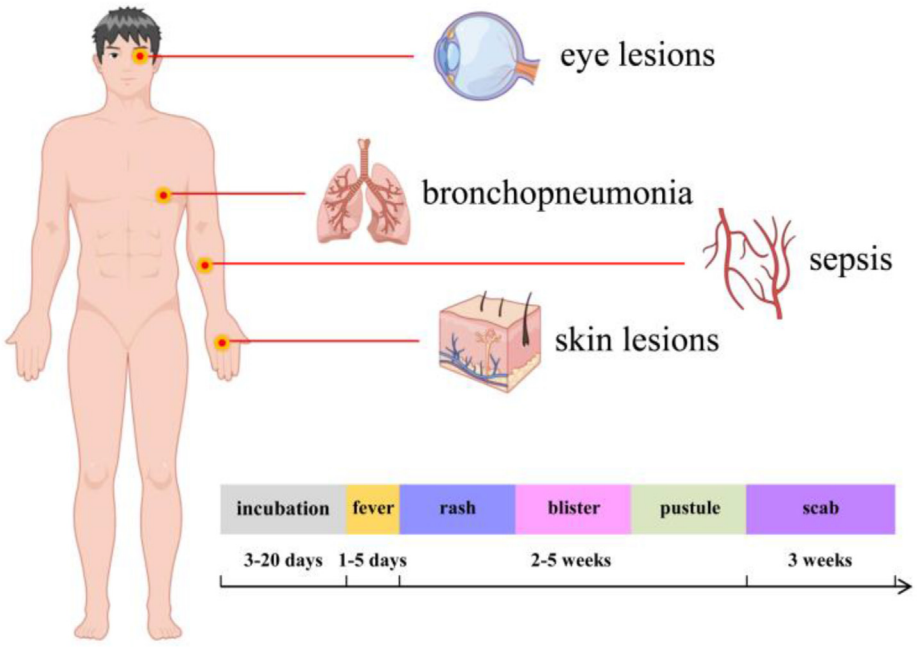

Figure 1. Clinical symptoms, complications of monkeypox, and progression of monkeypox symptoms.

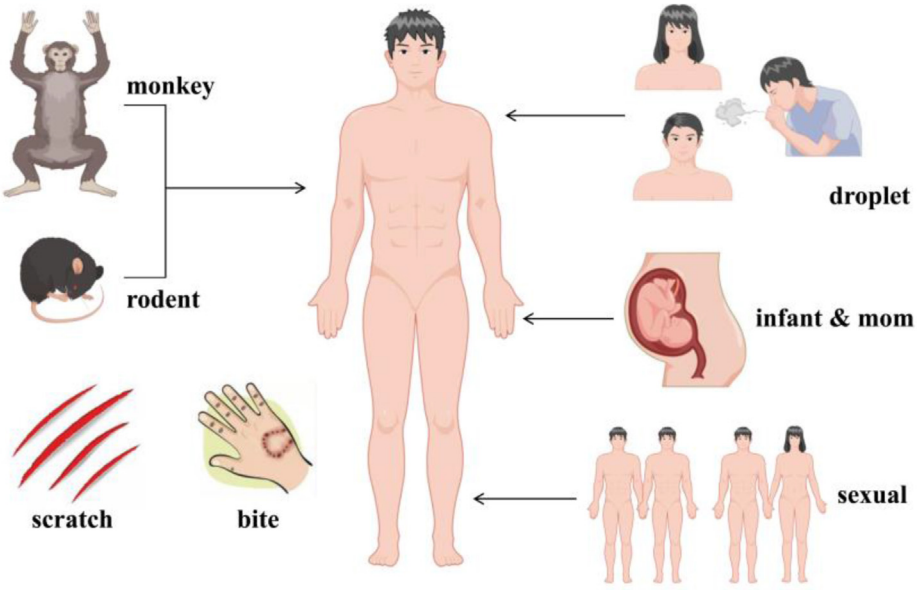

Figure 2. Transmission route of monkeypox: animal-human and human-human transmission route.

Severe cases of monkeypox infections are more common in children, immunocompromised individuals and those with preexisting conditions, which influence the degree of exposure to the virus and the severity of complications. While the current outbreak shows a low mortality rate from monkeypox, it remains a serious threat to public health. The World Health Organization (WHO) stated that the emergence of monkeypox cases in multiple non-manifold countries not directly linked to travel to monkeypox-endemic areas is atypical.[19] In recent years, the epidemiology situation of monkeypox has changed, the scope of its emergence has expanded, and the infectivity has increased significantly. In an effort to prevent monkeypox from becoming a global pandemic, it is imperative to develop vaccines and drugs that can prevent or treat monkeypox.

Prevention, treatment, and therapeutic effects

Variola, vaccinia, and monkeypox viruses belong to the genus Orthopoxvirus. Due to the presence of common antigens, variola and monkeypox can be prevented by vaccination. Recent studies have shown that the vaccinia vaccine, which has been reported to protect against

smallpox, can also protect against monkeypox virus. On the basis of these vaccines, researchers have improved the vaccine through genetic recombination and other ways to greatly improve the effectiveness of the vaccine and reduce the toxic side effects of the vaccine. In addition, because vaccines only work well before the virus is infected, efforts are also being made to develop antiviral drugs that can treat patients after exposure to the virus. Some of the current studies on monkeypox vaccine and antiviral therapy are summarized in Table 1.

Preventive effects of Vaccines

Vaccine played a crucial role in the eradication of smallpox, and studies have found that approved smallpox vaccines also provide some cross-protection against monkeypox.[20] Relevant vaccines are known to bind T cells to antigen presenting cells, activate B lymphocytes to produce antibodies, and promote cytotoxic T cells to clear virus-infected cells. The detailed mechanism of action is shown in Fig. 3. However, since smallpox was eradicated 30 years ago, the majority of the global population has not been vaccinated against smallpox. Therefore, it is possible that the resistance to orthopoxvirus has weakened. The WHO has given a series of specific recommendations for monkeypox prevention and control, the most important of which is to accelerate research on the use of a vaccine.[21] Given there is only one company in the world that manufactures monkeypox vaccines, acquiring a large supply in a short period of time would be a challenge. These circumstances have driven further optimization of existing smallpox vaccines and research into new vaccines that mitigate the toxic side effects of existing vaccines.

Because orthopoxviruses all have similar genetic properties, a vaccine that protects against a known poxvirus may also protect against other poxviruses.[22] Franceschi et al. designed a recombinant bovine herpesvirus 4 (BOHV-4) gene vaccine containing three monkeypox antigen proteins (A29L, M1R and B6R) with the goal of studying cowpox and smallpox attenuated vaccine.[23] It was found that mice treated with the three recombinant vaccines had no adverse reactions. The combined use of these vaccines

Table 1 Current research on monkeypox virus vaccine and antiviral therapy.

Protected mode	Animal model	Mechanism	Preventive or therapeutic effect	Reference
Recombinant vaccine	STAT1(−/−) mice	Construction of vaccine based on BoHV-4 vector	100 % alone protected STAT1(−/−) mice from death caused by monkeypox virus infection	23
Attenuated vaccine	Monkeys were immunized with LC16m8 or Lister	Mutation of immunogenic membrane protein B5R	The immunized monkeys did not develop monkeypox symptoms	25
Attenuated vaccine	Monkeys	Mutation of immunogenic membrane protein B5R	The vaccinated monkeys showed few monkeypox symptoms and provided long-term protection against viral infection	26
Attenuated vaccine	Cynomolgus macaque	Specific T cell and antibody response	Antibody binding titer and T-cell response of the Ankara vaccine were equal to or greater than the Dryvax vaccine alone	27—29
Recombinant vaccine	Mouse	The human IL-15 cytokine was integrated into the genome of the Wyeth vaccinia strain	The vaccinated mice developed superior immunogenicity	30,31
Modified vaccine	Rhesus monkeys	It works by encoding IFNα/βBP	No live virus was recovered after vaccination, and high concentrations of neutralizing and IgG antibodies were detected	32
Antiviral drug	Immunodeficient mouse	Blocking the maturation of the virus into the envelope	The virus could be inhibited from spreading to internal organs	36—43
Antiviral drug	Cynomolgus monkey	Broad-spectrum activity against DNA viruses (such as orthopoxvirus)	Plasma viral load decreased significantly	44,45
Antiviral drug	African green monkeys	Inhibition of intracellular guanosine triphosphate pool	Monkeypox virus replication is inhibited	46,47

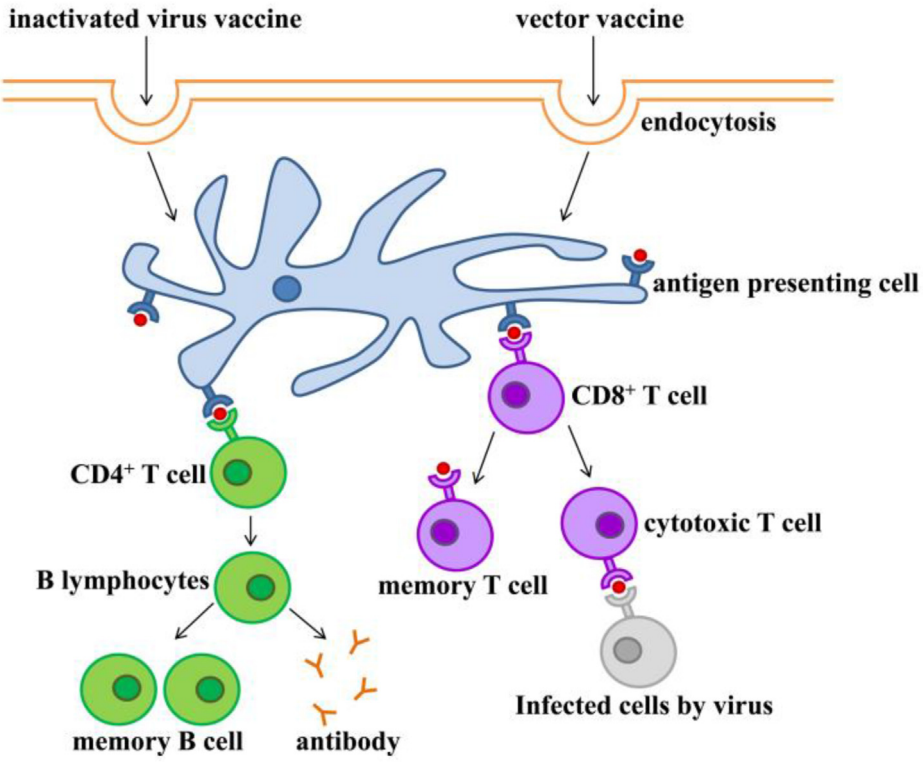

Figure 3. The mechanism of action of vaccines.

could protect STAT1 knockout mice against monkeypox virus 100 %.[23]

An increasing number of researchers have been working on another smallpox attenuated vaccine, LC16m8. Kennedy et al. explored the neutralization titer and immune response of LC16m8 to monkeypox by enzyme-linked immunosorbent assay and lymphocyte proliferation assay.[24] It was found that the LC16m8 vaccine not only produced neutralizing antibody titers against monkeypox virus, but it also produced a strong cellular immune response. Saijo et al. treated monkeys infected with monkeypox virus intranasally, which were closer to the natural route of infection, with the LC16m8 vaccine. They found that these model animals did not develop monkeypox symptoms.[25] They also treated monkeys that had been infected with monkeypox subcutaneously with the LC16m8 vaccine. They discovered that the immunized monkeys developed mild symptoms only in the site where the virus was inoculated and no symptoms elsewhere. Iizuka et al. evaluated the long-term efficacy of LC16m8 inoculation in an animal model infected with monkeypox.[26] Monkeys infected with monkeypox at six and twelve months after vaccination with LC16m8 were found to have few symptoms associated with monkeypox infection. These finding supported LC16m8 having a protective memory immune response against monkeypox virus. A single dose of LC16m8 provided lasting protection for more than one year after monkeypox infection in monkeys. These results demonstrated that LC16m8 vaccine, as a vaccinia-derived smallpox vaccine, could also protect humans from monkeypox damage.

While traditional smallpox vaccines, based on replicative vaccinia viruses, are effective, they may produce rare, but serious, side effects in immunocompromised individuals.[27,28] Moreover, pericarditis may occur as a complication in healthy individuals who have received conventional smallpox vaccines. These risks support the need to develop a safer vaccine. The modified vaccinia Ankara, as a highly attenuated replication deficient strain, has been widely studied by scholars. Stittelaar et al. investigated the efficacy of the Ankara vaccine in the cynomolgus macaque model and found that the animal model vaccinated with the Ankara vaccine produced heterologous T cells and antibody responses. In addition, the vaccine protected rhesus monkeys from the lethal and sublethal challenge of respiratory infection with monkeypox.[27] Earl et al. compared the Ankara vaccine with the Dryvax vaccine in a monkey model and found that the antibody binding titer and T-cell response of the Ankara vaccine were equal to or greater than the Dryvax vaccine alone whether it was used alone or in combination with Dryvax vaccine.[28] Zaeck et al. evaluated the efficacy of the Ankara vaccine in the population by analyzing reactive binding antibodies and neutralizing antibodies in populations vaccinated against smallpox, MPXV PCR-positive, vaccinated against MVA-BN-vaccinated, and MVA-H5-vaccinated individuals.[29] MPXV-neutralizing antibodies were found to be detectable in individuals after MPXV infection and after smallpox vaccination. It is worth noting that the neutralizing antibody response produced after two vaccinations are relatively low, and the third vaccination enhances the binding and neutralizing antibody response.

Cytokines secreted by mononuclear macrophages have a powerful effect on antiviral infection. Among them, type I cytokines can inhibit the enzyme that cells synthesize DNA and RNA virus replication, thus interfering with virus replication. Zielinski et al. integrated human IL-15 cytokine into the genome of the Wyeth vaccinia strain and found that vaccinated mice produced superior immunogenicity.[30] In addition, three years after Wyeth/IL-15 vaccination, there were no deaths in the vaccinated monkeys and fewer skin lesions in the animals. Hatch et al. chose to establish a cynomolgus macaque model to compare the preventive and therapeutic effects of two vaccines combined (Imvamune and ACAM2000) against monkeypox.[31] The results showed that rhesus monkeys vaccinated with the Imvamune vaccine alone failed to avoid virus infection and invasion. However, when rhesus monkeys were vaccinated with the ACAM2000 vaccine alone, no live virus was recovered and high concentrations of neutralizing and IgG antibodies were detected. Montanuy et al. found that three generations of smallpox vaccines (Dryvax, ACAM2000, and Ankara) all act by coding for IFNα/βBP.[32] In subsequent studies, they identified the binding site of IFNα/βBP interacting with cell surface in monkeypox by combining site-directed mutagenesis and other techniques. These findings are important for improving vaccine design.

Other researchers have been focusing on genetically engineered vaccines. Hooper et al. showed that mice immunized with vaccines that combined VACV LIR and A33R genes were more protective against poxvirus challenge. They also investigated the protection of mice with vaccines containing the A27L and B5R genes.[33] After reaching similar conclusions as in their previous study, they further combined the four genes and inoculated them into rhesus monkeys. They found that the four gene combination vaccine elicited antibody responses that crossed with homologous proteins of monkeypox. This demonstrated the potential for the gene combination vaccine to prevent monkeypox. Hooper et al. constructed a DNA vaccine against four known vaccinia virus genes (L1R, A27L, A33R, and B5R) and administered the vaccine to rhesus monkeys before exposure to monkeypox.[34] They found that a single gene vaccine based on one of the four genes kept monkeys alive, but not protected them from monkeypox, presumably by producing small amounts of neutralizing antibodies that would reduce the effective dose of the virus. However, when the monkeys were vaccinated with four genes homologous to monkeypox, the effectiveness of the vaccine was significantly increased, and no virus was detected in the monkeys' oral secretions. These findings support the potential for multicomponent mixtures of vaccine antigens to play an important role in protecting against poxviruses. Hirao et al. set up experimental groups for eight different DNA-encoded antigens (A4L, A27L, A33R, A56R, B5R, F9L, H3L, and L1R) and found that five of the antigens in the eight genes produced high antibody responses in macaques, which was consistent with the conclusion of Hooper et al.[35]

Therapeutic effects of Antiviral drugs

Vaccination that provides protection against monkeypox would be an accepted method of prevention or treatment before infection with the virus. However, at present, there is no effective, safe, and widely available treatment for monkeypox infection. In lieu of the availability of a vaccine, the use of antiviral drugs is being evaluated. ST-246 is a small molecule inhibitor against vaccinia virus homologues that safely and effectively prevents death from viral infection by blocking intracellular maturation of the virus to envelope, as shown in Fig. 4. It has been shown to have potent antiviral activity, preventing severe disease and death caused by vaccinia, smallpox and monkeypox viral infections in different animals through different routes.[36–43]

Grosenbach et al. analyzed and evaluated the efficacy of ST-246 through the immunodeficient mouse model. They found that in all the immunodeficient models they used, as long as T cells were intact and the mice were treated with ST-246 immediately after being infected with poxvirus, the virus could be inhibited from spreading to internal organs. ST-246 played a protective role for the host.[36] Berhanu et al. found that by treating infected mice intranasally with ST-246, there was a 22-fold reduction in virus shedding from the nasal mucosa and a 528-fold reduction in virus shedding from the lung mucosa, as compared with untreated mice. This demonstrated that the spread of the virus from the infection site to the internal organs was inhibited after treatment.[37] Smith et al. evaluated the efficacy of ST-246 against monkeypox in a prairie dog model.[38] After testing blood samples and viral DNA of animals treated with ST-246, it was determined that the treatment was 100 % effective in preventing the death of animals after skin rash symptoms. In addition, no viral DNA was detected in animals treated immediately before the onset of symptoms and most did not develop symptoms.

Smith et al. found that ST-246 had an effective concentration of 0.015–0.05 μm against monkeypox virus in vitro.[39] Jordan et al. treated cynomolgus monkeys with different concentrations of ST-246 after three days of monkeypox infection. It was determined that the minimum effective dose of ST-246 for 100 % protection against monkeypox was 10 mg/kg/day, which was assumed to be equivalent to 400 mg daily in humans.[40] Huggins et al. suggested that continuous treatment with ST-246 at a dose of 300 mg/m^2/day for more than 10 days was the optimal dose to provide effective protection.[41] Sbrana et al. studied in a gopher model, using ST-246 at a dose of 100 mg/kg/day to treat gophers injected with lethal doses of monkeypox.[42] They found that 100 % of the animals who started treatment between days 0 and 3 after contracting the virus survived, and 67 % of the animals who started treatment on day 4 survived. By analyzing pharmacokinetic and pharmacodynamic models, Leeds et al. determined that the optimal effective dose of ST-246 for smallpox prevention in humans was 600 mg.[43]

Cidofovir is an acyclic nucleoside analogue with broad spectrum activity against DNA viruses, such as orthpoxviruses. Its anti-poxvirus activity has been demonstrated in infected animal models.[44] Stittelaar et al. evaluated the efficacy of cidofovir in a cynomolgus monkey model against a tracheal infection with virus and showed that all untreated animals died within 15 days of infection.[45] Only one animal inoculated with the positive control drug Elstree-RIVM survived. Animals inoculated with 5 mg/kg of

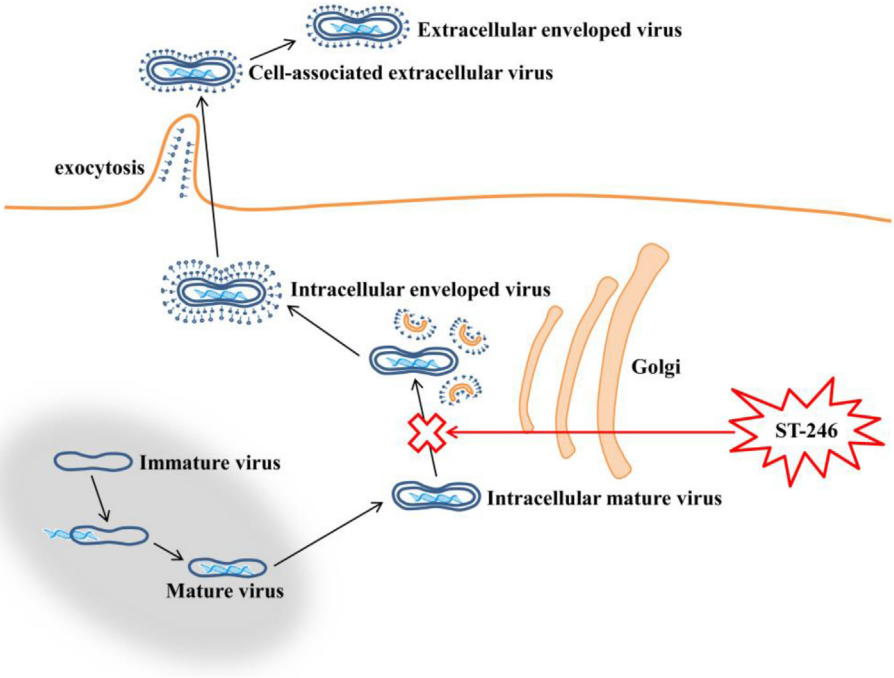

Figure 4. The mechanism of ST-246 blocking poxvirus synthesis.

cidofovir were survived and had significantly lower plasma viral loads. This suggested that earlier treatment after infection increased the chance of survival.

Smee et al. treated monkeypox infected African green monkeys and mouse models with mycophenolic acid (MPA) and ribavirin, respectively, and found that MPA inhibited monkeypox virus by 50 %.[46] The inhibition rate of ribavirin in mice was higher than that in African green monkeys. The mechanism of MPA and ribavirin was related to the inhibition of intracellular guanosine triphosphate pool. Baker et al. analyzed the effects of 24 antiviral compounds on monkeypox.[47] Eight of these compounds, including cidofovir and ribavirin, inhibited monkeypox replication at drug concentrations. The virus isolates were found to be most sensitive to three compounds: cidofovir, cHPMPC, and ribavirin.

With the development of DNA editing technology, the development of a direct antiviral therapy against monkeypox has become a significant avenue of research. Viral vectors that produce high viral titers and are safe are classified as effective vectors in antiviral therapy. Siegrist et al. integrated plasmids containing A17L, E3L, and 12L genes into human embryonic kidney cells by CRISPR-Cas9 and cell transfection technology.[48] After analyzing the effectiveness of the targets, they found that the viral titer of each gene target was reduced by 93.19 %. In addition, antiviral drugs coated with adenovirus as a vector also reduced the viral titer of each gene target by 92.97 % and had a protective effect on host cells.

Although vaccination was effective for monkeypox prevention prior to exposure to the virus, the vaccine effect was limited after exposure. Further research revealed that the combination of vaccine and antiviral drugs was an effective form of treatment. Tecovirimat is the active pharmaceutical ingredient in the smallpox antiviral drug TPOXX. Although the mechanism of action of the vaccine and the antiviral compound are different, the possibility of concurrent use cannot be ruled out. To investigate whether co-treatment with vaccines and antiviral agents would impact efficacy, Russo et al. used Tecovirimat in monkey models infected with monkeypox after Dryvax or ACAM2000 vaccination.[49] The results indicated that Tecovirimat had no effect on the protective immunity produced by the vaccine, and the severity and regression time of the lesions at the site of virus inoculation were reduced or shortened. Moreover, macaques that were vaccinated with ACAM2000 and treated with Tecovirimat after monkeypox infection survived. Berhanu et al. also investigated the effect of the combination of Tecovirimat and ACAM2000 and found that the ACAM2000 vaccine alone did not protect cynomolgus monkeys after the third day of monkeypox infection in this animal model.[50] However, Tecovirimat alone or in combination with ACAM2000 produced a potent protective effect, especially when the combination delayed treatment until days 4 and 5 with 83 % protection and day 6 with 50 % protection.

Alternative therapies

In addition to vaccines and antiviral drugs, researchers are discovering additional treatments for monkeypox. Alkhalil et al. explored the therapeutic effect of RNA interference pathway on monkeypox.[51] By developing 48 small interfering RNA and evaluating their ability to inhibit the virus, they found that two of the genes produced 65—95 % inhibition rates during the viral replication process without having toxic effects on cells. The E8L gene was involved in

the process of virus entry into cells and the A6R gene was involved in the process of virus replication. In addition, ten nM A6R-siRNA could inhibit virus replication for seven days.

It has been shown that the introduction of interferon has a protective effect on poxvirus infected animals, and Johnston et al. continued to use IFN-β to explore its therapeutic potential against monkeypox.[52] Their research has shown that IFN-β can inhibit monkeypox production and transmission by inducing the expression of antiviral proteins in virus-infected cells within six to 8 h of viral infection. In previous studies, the antiviral protein, MxA, has also been shown to work against a variety of viruses, including monkeypox.[53] MxA protein was found in the virus envelope in monkeypox-infected cells. The specific mechanism of action remains to be studied.

Conclusion

As the climate and environment change, both animals and humans are changing their living habitats, and many diseases that were originally transmitted between animals can also be transmitted to humans. In areas of Africa where humans are in close contact with wildlife, monkeypox is not only a serious public health threat, but it is a deadly infectious disease with the ability to mutate. After the smallpox vaccine was no longer widely applied globally, the population's resistance to orthopoxvirus decreased over time, and there was a significant upward trend in the frequency and geographical distribution of the disease in recent years. At present, the host and mode of transmission of monkeypox virus are unknown, there is a lack of effective prevention and treatment methods, few vaccines have been approved, and the specific mechanism of effective antiviral drugs requires further study. There is a need to accelerate the development of new vaccines and antiviral drugs. In addition, stronger prevention measures are warranted, and more robust diagnostic tools are needed in identifying monkeypox in an effort to control further spread of the virus. In addition, there is a need to understand how monkeypox virus persists in nature and explore its impact on ecological factors in an effort to control monkeypox outbreaks.

Author contributions

Conception and design of study: Y.H. Luo, T. Zhang, C.H. Jin; Acquisition of data: T. Zhang, J.L. Cao, A.Q. Wang; Data analysis and/or interpretation: Y.H. Luo, W.S. Hou; Drafting of manuscript and/or critical revision: Y.H. Luo, T. Zhang, C.H. Jin; Approval of final version of manuscript: Y.H. Luo, T. Zhang, J.L. Cao, W.S. Hou, A.Q. Wang, C.H. Jin.

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Conflicts of interest

The authors declare they have no conflict of interest.

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References

1. McCarthy MW. Recent advances in the diagnosis monkeypox: implications for public health. *Expert Rev Mol Diagn* 2022;**24**:1—6.
2. Silva NIO, de Oliveira JS, Kroon EG, Trindade GS, Drumond BP. Here, there, and everywhere: the wide host range and geographic distribution of zoonotic orthopoxviruses. *Viruses* 2020;**13**(1):43.
3. Bunge EM, Hoet B, Chen L, Lienert F, Weidenthaler H, Baer LR, et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. *PLoS Neglected Trop Dis* 2022;**16**(2):e0010141.
4. Khamees A, Awadi S, Al-Shami K, Alkhoun HA, Al-Eitan SF, Alsheikh AM, et al. Human monkeypox virus in the shadow of the COVID-19 pandemic. *Journal of infection and public health* 2023;**16**(8):1149—57.
5. Petersen E, Kantele A, Koopmans M, Asogun D, Yinka-Ogunleye A, Ihekweazu C, et al. Human monkeypox: epidemiologic and clinical characteristics, diagnosis, and prevention. *Infect Dis Clin* 2019;**33**(4):1027—43.
6. Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, et al. Monkeypox virus infection in humans across 16 countries - April-June 2022. *N Engl J Med* 2022;**387**(8):679—91.
7. Kumar N, Acharya A, Gendelman HE, Byrareddy SN. The 2022 outbreak and the pathobiology of the monkeypox virus. *J Autoimmun* 2022;**131**:102855.
8. Beer EM, Rao VB. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. *PLoS Neglected Trop Dis* 2019;**13**(10):e0007791.
9. Li Y, Olson VA, Laue T, Laker MT, Damon IK. Detection of monkeypox virus with real-time PCR assays. *J Clin Virol* 2006;**36**(3):194—203.
10. Simpson K, Heymann D, Brown CS, Edmunds WJ, Elsgaard J, Fine P, et al. Human monkeypox - after 40 years, an unintended consequence of smallpox eradication. *Vaccine* 2020;**38**(33):5077—81.
11. Focosi D, Novazzi F, Baj A, Maggi F. Monkeypox: an international epidemic. *Rev Med Virol* 2022:e2392.
12. Sah R, Abdelaal A, Reda A, Katamesh BE, Manirambona E, Abdelmonem H, et al. Monkeypox and its possible sexual transmission: where are we now with its evidence? *Pathogens* 2022;**11**(8):924.
13. Huang ST, Wu YH, Lin HH, Yang JY, Hsieh PY, Chiang SJ, et al. The first imported case of monkeypox in Taiwan. *Journal of the Formosan Medical Association = Taiwan yi zhi* 2023;**122**(1):73—7.
14. Hraib M, Jouni S, Albitar MM, Alaidi S, Alshehabi Z. The outbreak of monkeypox 2022: an overview. *Ann Med Surg (Lond)* 2022;**79**:104069.

15. Khodakevich L, Jezek Z, Messinger D. Monkeypox virus: ecology and public health significance. *Bull World Health Organ* 1988; **66**(6):747—52.
16. Vaughan A, Aarons E, Astbury J, Brooks T, Chand M, Flegg P, et al. Human-to-Human transmission of monkeypox virus, United Kingdom. *Emerg Infect Dis* 2020;**26**(4):782—5. October 2018.
17. Pastula DM, Tyler KL. An overview of monkeypox virus and its neuroinvasive potential. *Ann Neurol* 2022;**92**(4):527—31.
18. Aljabali AA, Obeid MA, Nusair MB, Hmedat A, Tambuwala MM. Monkeypox virus: an emerging epidemic. *Microb Pathog* 2022; **173**:105794.
19. Parums DV. Editorial: current status of non-endemic global infections with the monkeypox virus. *Med Sci Mon Int Med J Exp Clin Res* 2022;**28**:e938203.
20. Parker S, Nuara A, Buller RM, Schultz DA. Human monkeypox: an emerging zoonotic disease. *Future Microbiol* 2007;**2**(1): 17—34.
21. Smallpox. post-eradication vigilance continues. *WHO Chron* 1982;**36**(3):87—91.
22. Miller L, Richter M, Hapke C, Stern D, Nitsche A. Genomic expression libraries for the identification of cross-reactive orthopoxvirus antigens. *PLoS One* 2011;**6**(7):e21950.
23. Franceschi V, Parker S, Jacca S, Crump RW, Doronin K, Hembrador E, et al. BoHV-4-Based vector single heterologous antigen delivery protects STAT1(-/-) mice from monkeypoxvirus lethal challenge. *PLoS Neglected Trop Dis* 2015; **9**(6):e0003850.
24. Kennedy JS, Gurwith M, Dekker CL, Frey SE, Edwards KM, Kenner J, et al. Safety and immunogenicity of LC16m8, an attenuated smallpox vaccine in vaccinia-naive adults. *J Infect Dis* 2011;**204**(9):1395—402.
25. Saijo M, Ami Y, Suzaki Y, Nagata N, Iwata N, Hasegawa H, et al. LC16m8, a highly attenuated vaccinia virus vaccine lacking expression of the membrane protein B5R, protects monkeys from monkeypox. *J Virol* 2006;**80**(11):5179—88.
26. Iizuka I, Ami Y, Suzaki Y, Nagata N, Fukushi S, Ogata M, et al. A single vaccination of nonhuman primates with highly attenuated smallpox vaccine, LC16m8, provides long-term protection against monkeypox. *Jpn J Infect Dis* 2017;**70**(4):408—15.
27. Stittelaar KJ, van Amerongen G, Kondova I, Kuiken T, van Lavieren RF, Pistoor FH, et al. Modified vaccinia virus Ankara protects macaques against respiratory challenge with monkeypox virus. *J Virol* 2005;**79**(12):7845—51.
28. Earl PL, Americo JL, Wyatt LS, Eller LA, Whitbeck JC, Cohen GH, et al. Immunogenicity of a highly attenuated MVA smallpox vaccine and protection against monkeypox. *Nature* 2004;**428**(6979):182—5.
29. Zaeck LM, Lamers MM, Verstrepen BE, Bestebroer TM, van Royen ME, Götz H, et al. Low levels of monkeypox virus-neutralizing antibodies after MVA-BN vaccination in healthy individuals. *Nat Med* 2023;**29**(1):270—8.
30. Zielinski RJ, Smedley JV, Perera PY, Silvera PM, Waldmann TA, Capala J, et al. Smallpox vaccine with integrated IL-15 demonstrates enhanced in vivo viral clearance in immunodeficient mice and confers long term protection against a lethal monkeypox challenge in cynomolgus monkeys. *Vaccine* 2010; **28**(43):7081—91.
31. Hatch GJ, Graham VA, Bewley KR, Tree JA, Dennis M, Taylor I, et al. Assessment of the protective effect of Imvamune and Acam2000 vaccines against aerosolized monkeypox virus in cynomolgus macaques. *J Virol* 2013;**87**(14):7805—15.
32. Montanuy I, Alejo A, Alcami A. Glycosaminoglycans mediate retention of the poxvirus type I interferon binding protein at the cell surface to locally block interferon antiviral responses. *FASEB J* 2011;**25**(6):1960—71.
33. Hooper JW, Custer DM, Thompson E. Four-gene-combination DNA vaccine protects mice against a lethal vaccinia virus challenge and elicits appropriate antibody responses in nonhuman primates. *Virology* 2003;**306**(1):181—95.
34. Hooper JW, Thompson E, Wilhelmsen C, Zimmerman M, Ichou MA, Steffen SE, et al. Smallpox DNA vaccine protects nonhuman primates against lethal monkeypox. *J Virol* 2004; **78**(9):4433—43.
35. Hirao LA, Draghia-Akli R, Prigge JT, Yang M, Satishchandran A, Wu L, et al. Multivalent smallpox DNA vaccine delivered by intradermal electroporation drives protective immunity in nonhuman primates against lethal monkeypox challenge. *J Infect Dis* 2011;**203**(1):95—102.
36. Grosenbach DW, Berhanu A, King DS, Mosier S, Jones KF, Jordan RA, et al. Efficacy of ST-246 versus lethal poxvirus challenge in immunodeficient mice. *Proc Natl Acad Sci U S A* 2010;**107**(2):838—43.
37. Berhanu A, King DS, Mosier S, Jordan R, Jones KF, Hruby DE, et al. ST-246 inhibits in vivo poxvirus dissemination, virus shedding, and systemic disease manifestation. *Antimicrob Agents Chemother* 2009;**53**(12):4999—5009.
38. Smith SK, Self J, Weiss S, Carroll D, Braden Z, Regnery RL, et al. Effective antiviral treatment of systemic orthopoxvirus disease: ST-246 treatment of prairie dogs infected with monkeypox virus. *J Virol* 2011;**85**(17):9176—87.
39. Smith SK, Olson VA, Karem KL, Jordan R, Hruby DE, Damon IK. In vitro efficacy of ST246 against smallpox and monkeypox. *Antimicrob Agents Chemother* 2009;**53**(3):1007—12.
40. Jordan R, Goff A, Frimm A, Corrado ML, Hensley LE, Byrd CM, et al. ST-246 antiviral efficacy in a nonhuman primate monkeypox model: determination of the minimal effective dose and human dose justification. *Antimicrob Agents Chemother* 2009;**53**(5):1817—22.
41. Huggins J, Goff A, Hensley L, Mucker E, Shamblin J, Wlazlowski C, et al. Nonhuman primates are protected from smallpox virus or monkeypox virus challenges by the antiviral drug ST-246. *Antimicrob Agents Chemother* 2009;**53**(6):2620—5.
42. Sbrana E, Jordan R, Hruby DE, Mateo RI, Xiao SY, Siirin M, et al. Efficacy of the antipoxvirus compound ST-246 for treatment of severe orthopoxvirus infection. *Am J Trop Med Hyg* 2007;**76**(4): 768—73.
43. Leeds JM, Fenneteau F, Gosselin NH, Mouksassi MS, Kassir N, Marier JF, et al. Pharmacokinetic and pharmacodynamic modeling to determine the dose of ST-246 to protect against smallpox in humans. *Antimicrob Agents Chemother* 2013; **57**(3):1136—43.
44. Andrei G, Snoeck R. Cidofovir activity against poxvirus infections. *Viruses* 2010;**2**(12):2803—30.
45. Stittelaar KJ, Neyts J, Naesens L, van Amerongen G, van Lavieren RF, Holý A, et al. Antiviral treatment is more effective than smallpox vaccination upon lethal monkeypox virus infection. *Nature* 2006;**439**(7077):745—8.
46. Smee DF, Bray M, Huggins JW. Antiviral activity and mode of action studies of ribavirin and mycophenolic acid against orthopoxviruses in vitro. *Antivir Chem Chemother* 2001;**12**(6): 327—35.
47. Baker RO, Bray M, Huggins JW. Potential antiviral therapeutics for smallpox, monkeypox and other orthopoxvirus infections. *Antivir Res* 2003;**57**(1—2):13—23.
48. Siegrist CM, Kinahan SM, Settecerri T, Greene AC, Santarpia JL. CRISPR/Cas9 as an antiviral against Orthopoxviruses using an AAV vector. *Sci Rep* 2020;**10**(1):19307.
49. Russo AT, Berhanu A, Bigger CB, Prigge J, Silvera PM, Grosenbach DW, et al. Co-administration of tecovirimat and ACAM2000™ in non-human primates: effect of tecovirimat treatment on ACAM2000 immunogenicity and efficacy versus lethal monkeypox virus challenge. *Vaccine* 2020;**38**(3): 644—54.
50. Berhanu A, Prigge JT, Silvera PM, Honeychurch KM, Hruby DE, Grosenbach DW. Treatment with the smallpox antiviral

tecovirimat (ST-246) alone or in combination with ACAM2000 vaccination is effective as a postsymptomatic therapy for monkeypox virus infection. *Antimicrob Agents Chemother* 2015;**59**(7):4296—300.

51. Alkhalil A, Strand S, Mucker E, Huggins JW, Jahrling PB, Ibrahim SM. Inhibition of monkeypox virus replication by RNA interference. *Virol J* 2009;**6**:188.
52. Johnston SC, Lin KL, Connor JH, Ruthel G, Goff A, Hensley LE. In vitro inhibition of monkeypox virus production and spread by Interferon-β. *Virol J* 2012;**9**:5.
53. Haller O, Gao S, von der Malsburg A, Daumke O, Kochs G. Dynamin-like MxA GTPase: structural insights into oligomerization and implications for antiviral activity. *J Biol Chem* 2010; **285**:28419—24.