Cell Insight 3 (2024) 100185

Contents lists available at ScienceDirect

Cell Insight

journal homepage: www.journals.elsevier.com/cell-insight

Review

The monkeypox virus-host interplays

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ARTICLE INFO

Keywords:
Monkeypox virus
Antiviral immunity
Immune evasion
Pathogenicity

ABSTRACT

Monkeypox virus (MPXV) is a DNA virus belonging to the *Orthopoxvirus* genus within the Poxviridae family which can cause a zoonotic infection. The unexpected non-endemic outbreak of mpox in 2022 is considered as a new global threat. It is imperative to take proactive measures, including enhancing our understanding of MPXV's biology and pathogenesis, and developing novel antiviral strategies. The host immune responses play critical roles in defensing against MPXV infection while the virus has also evolved multiple strategies for immune escape. This review summarizes the biological features, antiviral immunity, immune evasion mechanisms, pathogenicity, and prevention strategies for MPXV.

1. Introduction

Monkeypox virus (MPXV) is a double-stranded (ds) DNA virus of the *Orthopoxvirus* genus within the Poxviridae family. *Orthopoxvirus* genus pathogenic for humans also includes variola virus (VARV), vaccinia virus (VACV), and cowpox virus (CPXV) (El Eid et al., 2022). MPXV was firstly identified in 1958 from crab-eating monkeys (*Macaca fascicularis*) in Copenhagen (Cop), Denmark. The first recorded human case of MPXV infection occurred in the Democratic Republic of the Congo in 1970 (Mileto et al., 2022).

Mpox, a rare zoonotic infectious disease caused by MPXV, primarily affects Central and West Africa. Based on genetic and geographic variation, MPXV has been divided into two main genetic clades: Clade I (formerly Congo Basin clade) is prevalent in Central Africa and associated with a more severe form of the disease and higher mortality. Clade II (formerly West African clade), endemic in West Africa, including subclades IIa and IIb, is associated with milder disease and a lower mortality rate (Bunge et al., 2022). Mpox symptoms closely resemble those of smallpox, but the disease is generally milder, typically manifesting as high fever, headache, lymphadenopathy, muscle aches, and rashes (Petersen et al., 2019). Individuals with compromised immune systems, especially children, develop severe diseases with a fatality rate ranging from 1% to 10% (Gong et al., 2022). Since the eradication of smallpox, mpox has emerged as one of the most significant infectious diseases caused by a poxvirus.

The unexpected non-endemic outbreak of mpox in 2022 is considered as a new global threat after coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This has prompted the World Health Organization (WHO) to declare mpox as a Public Health Emergency of International Concern (Li et al., 2022). Although vaccine for smallpox is 85% effective against MPXV, it has been discontinued for decades since the eradication of smallpox in 1980 (Fine et al., 1988; Li et al., 2022). Despite being the second most pathogenic poxvirus after VARV, the research on mpox and MPXV is under developed. A thorough understanding of the biological characteristics, pathogenic mechanisms, and prevention and control strategies of MPXV is essential for developing more effective strategies to prevent mpox outbreak. In the current review, we will discuss multifaceted aspects of the neglected zoonotic pathogen with an emphasis on host immunity and immune evasion.

1.1. Viral genome and structure

The genome of the reference strain, Central African MPXV Zaire strain (NC_003310.1) (Clade I), comprises about 197 kb of dsDNA encoding more than 190 open reading frames (ORFs). A significant portion of these ORFs is poorly characterized (Forni et al., 2022; Kugelman et al., 2014). Despite a relatively small genomic sequence difference of approximately 0.55–0.56% between MPXV clade I and II (Chen et al., 2005), variations in crucial regions encoding important virulence genes likely explain the observed differences in disease severity between the two clades (Estep et al., 2011; Hudson et al., 2012). The coding region of the MPXV genome

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https://doi.org/10.1016/j.cellin.2024.100185
Received 6 March 2024; Received in revised form 11 July 2024; Accepted 11 July 2024
Available online 14 July 2024

is highly conserved with those of orthopoxviruses, which encodes essential components involved in viral replication, transcription, and virion assembly (Karagoz et al., 2023; Shchelkunov et al., 2001, 2002). The variable regions at extremities of the viral genome contain identical but opposite sequences called inverted terminal repeats (ITRs), which are prone to the formation of covalently closed hairpin ends and critically involved in host range and pathogenicity among poxviruses (Haller et al., 2014; Lefkowitz et al., 2006; Shchelkunov et al., 2002). Although poxviruses share a similar genome composition, apparent variations occur across different poxviruses (Lefkowitz et al., 2006). The plasticity of poxvirus genomes is most evident in ITR regions (Haller et al., 2014; Hendrickson et al., 2010). The MPXV Clade I and II exhibit significant differences in deletions and insertions within the ITR regions (Chen et al., 2005), which is also evident in sequences of MPXV isolates from the U.S. outbreak in 2003 (Likos et al., 2005). Sequence analyses of isolated virus strains from the 2022 outbreak reveal a significantly higher number of G to A mutations within the apolipoprotein B mRNA editing catalytic polypeptide-like 3 (APOBEC3) context compared to previously isolated strains. Notably, the vast majority (95%, or 156 out of 167 mutations) are specifically GA-to-AA substitutions. These mutations are indicative of the action of APOBEC3 cytosine deaminase, a host antiviral enzyme, as well as sustained human-to-human transmission (Gigante et al., 2022; O'Toole et al., 2023). Consistent with this finding, a study of MPXV genomes from southern Nigerian patients in 2019–2020 reveals the co-circulation of multiple MPXV variants in humans in West Africa before 2022, with a pattern of APOBEC3-mediated mutations (Ndodo et al., 2023). The mutation rate, adaptability, and ongoing genetic evolution of MPXV are key factors contributing to its heightened transmissibility, virulence, and ability to evade immune responses, potentially leading to a surge in cases worldwide (Karagoz et al., 2023).

Like other poxviruses, MPXV is a large virus ranging from 200 to 250 nm in size, which exhibits an oval, rounded, or brick-shaped morphology. The virion of MPXV consists of a double-concave dumbbell-shaped core, lipoprotein membrane, lateral bodies, surface tubules, and dsDNA (Li et al., 2023). The core area of MPXV virion encapsulates enzymes associated with the primary transcription of structural genes (Kmiec & Kirchhoff, 2022). The genome and structure of MPXV are shown in Fig. 1.

2. The infection and life cycle of MPXV

MPXV exhibits a broad host range, encompassing rodents, humans, and nonhuman primates (Doty et al., 2017). Notably, it primarily infects oral and respiratory mucosal and epithelial tissues, followed by dissemination to regional lymph nodes and potential involvement of other organs like the spleen and liver (Moulton et al., 2008; Zaucha et al., 2001). MPXV transmission has been observed among the men who have sex with men (MSM) in the 2022 outbreak. Close contact during sexual activity

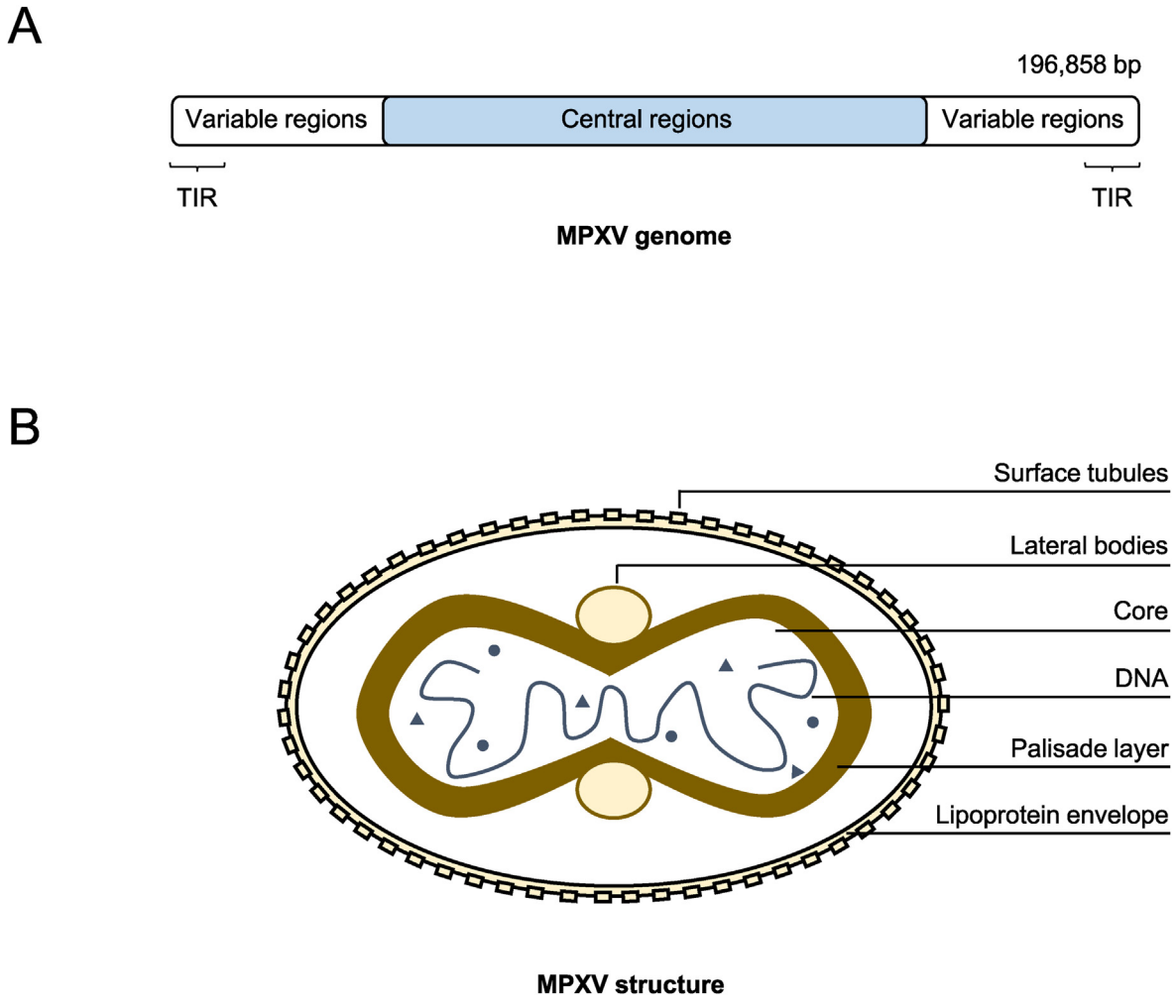

Fig. 1. MPXV Genome and structure
(A) The MPXV genome has a large, conserved central region encoding essential factors. Flanking this core are two variable regions with identical but opposite sequences at their ends, known as ITRs. (B) The MPXV is made up of five main parts: a double-concave dumbbell-shaped core, lipoprotein membrane, lateral bodies, surface tubules and its genomic DNA.

appears to be a significant route of viral spread (Palich et al., 2023). MPXV infection primarily occurs in the forms of intracellular mature virions (IMVs) and extracellular enveloped virions (EEVs). These two forms exhibit different infectious properties and are widely used as antibody targets (Golden et al., 2011; Kumar et al., 2022; Li et al., 2022; Schramm & Locker, 2005). Similar to most other poxviruses, both MPXV particles complete their infection process through the following six steps: attachment, entry, transcription and translation, replication, assembly, and release (Aljabali et al., 2022; Greseth & Traktman, 2022; Schramm & Locker, 2005).

Based on previous studies on VACV infection, it is believed that attachment of MPXV is mediated by viral ligands, host receptors and other proteins involved in virus-host interaction (Hatmal et al., 2022; Quemin et al., 2018; Smith & Law, 2004). However, direct evidence for this mechanism is currently lacking. The attachment of poxviruses exemplified by VACV, to the host cell surface is mediated by at least four viral proteins, including D8, A27, A26, and H3 (unless otherwise specified, viral protein names in this text follow the VACV-WR designation) (Moss, 2016). Glycosaminoglycans located on host cell surface, such as chondroitin sulfate and heparin sulfate, have been implicated as receptors involved in viral attachment (Howard et al., 2008; Matho et al., 2018; Moss, 2016; Moulard & Decroly, 2000). After adsorption, MPXV enters the host cytoplasm by membrane fusion, micropinocytosis, or endocytosis. This process depends on an entry-fusion complex consisted of at least 11 conserved poxviral components, such as A28 and A21, and several host accessory proteins (Hatmal et al., 2022; Moss, 2012, 2016; Senkevich et al., 2005). Notably, Conserved Oligomeric Golgi (COG) complex, a vesicle comprised of eight proteins (COG1-COG8) in host cells, plays a critical role in viral entry and fusion, as evidenced by measurements of early gene expression and host fluorescence of DiD-labeled VACV, respectively. Specifically, knockout of each member of the COG1-COG8 complex significantly hinders VACV entry, while knockout of COG4 and COG7 impairs viral fusion. These effects have been further investigated in COG-rescued cell lines (Realegeno et al., 2017, 2020). Upon attaching to and fusing with the host cell, the virus swiftly discards its outer coat and begins expressing early genes. At the same time, the viral genome and multi-subunit DNA-dependent RNA polymerases are released for DNA replication and the transcription of intermediate and late genes (Altayb, 2022), which is dependent on the factors encoded by the early genes (Rubins et al., 2008). Interestingly, poxvirus initiates transcription of the early genes before the viral core is fully disassembled (Schmidt et al., 2013), which may be one way the virus achieves a rapid life cycle. Subsequently, MPXV DNA and late proteins assemble to form IMVs (Realegeno et al., 2017). A fraction of these IMVs is wrapped by double membranes originating from the ER or Golgi apparatus to form intracellular enveloped virions (IEVs) (Altayb, 2022; Li et al., 2022). IEVs fuse with the cellular inner membrane to form cell-associated enveloped virions (CEVs). Finally, CEVs are released into the extracellular environment to form EEVs (Hatmal et al., 2022). Infectious IMVs wrapped by a single membrane primarily mediate transmission by exiting through cell lysis, while EEVs comprised of triple membranes primarily spread to neighboring cells through exocytosis (Paniz-Mondolfi et al., 2023; Pickup, 2015). Although current research on poxviruses provides a general understanding of MPXV infection and its replication cycle, the exact viral proteins and host receptors involved in the MPXV life cycle remain to be fully elucidated.

An ideal animal model is necessary for comprehending the pathogenesis of MPXV. Conventional animal models, including guinea pigs, golden hamsters, and common mouse strains, are non-susceptibility to MPXV (Americo et al., 2023). It has been shown that a low-dose intranasal infection of STAT1-deficient C57BL/6 mice results in 100% mortality ten days after infection, with high viral titers detected in multiple organs of moribund animals (Stabenow et al., 2010). Additionally, the wild-derived castaneous (CAST/EiJ) mice exhibit exceptional vulnerability to MPXV infection following intranasal inoculation (Americo et al., 2023). Several wild-derived inbred strains including PERA/EiJ and MOLF/EiJ mice also show significant symptoms to MPXV infection (Wei et al., 2023). Therefore, the STAT1-deficient C57BL/6 mice and the wild-derived inbred CAST/EiJ, PERA/EiJ and MOLF/EiJ mice provide mouse models for investigating the immunological and pathogenic mechanisms of MPXV infection. Notably, due to an incomplete JAK/-STAT pathway, which is crucial for inhibiting viral infections, mouse strains lacking STAT1 are not suitable models for studying STAT1-mediated anti-poxvirus immune responses.

2.1. Host immunity

The host immune responses to MPXV play critical roles in disease pathogenesis and clinical manifestations (Li et al., 2023). Understanding these immune responses is essential for the prevention and control of viral spread. Here, we focus on the underlying mechanisms of host immunity to MPXV.

Numerous studies from *in vitro* and *in vivo* experiments to clinical trials have demonstrated that host cells initiate a series of immune responses to antagonize MPXV infection (Johnston et al., 2015; Li et al., 2023). The arm of innate immunity serves as the first line of antiviral defense and has been shown to significantly subvert virus replication and assembly during poxvirus infection (Li et al., 2023; Lu & Zhang, 2020; Lum et al., 2022). Adaptive immunity further eliminates viral particles by secreting neutralizing antibodies or employing cytotoxic immune cells to target virus-infected cells (Lum et al., 2022; Panchanathan et al., 2008).

Mucosal tissues and innate immune cells such as monocytes and natural killer (NK) cells are critically important for innate antiviral immunity by inducing type I interferons (IFNs) and inflammatory cytokines. Mucosal tissue is a primary site of MPXV infection, with a lesion rate of up to 41% in infected individuals (Thornhill et al., 2022). An increased production of calcium-binding proteins (S100A8, S100A9), critical components of mucosal immunity (Li et al., 2021; Willers et al., 2020), has been observed in MPXV-infected macaques (Brown et al., 2010). Monocytes are rapidly recruited to infection sites and directly kill infected cells once they sense MPXV intrusion, and their number increases sharply. However, monocytes are also susceptible to MPXV infection and can cross the blood-brain barrier, potentially resulting in neurological diseases (Sepehrinezhad et al., 2023; Song, Janosko, et al., 2013). NK cells, on the one hand, play a pivotal role in protecting CAST/EiJ mice from lethal MPXV infection (Earl et al., 2020), but on the other hand, MPXV suppresses the cytotoxicity and migratory capacity of NK cells in infected rhesus macaques (Song, Josleyn, et al., 2013).

Numerous cytokines and chemokines are induced upon MPXV infection. A serum cytokine profile derived from 19 individuals with confirmed MPXV disease shows elevated levels of Macrophage Inflammatory Proteins 1α (MIP-1α/CCL3) and 1β (MIP-1β/CCL4) in all stages of infection following MPXV exposure. MPXV infection causes a pronounced T helper type 2 (Th2) response characterized by elevated serum levels of Th2-associated cytokines, including interleukin-4 (IL-4), IL-5, IL-6, and IL-10. Conversely, the levels of Th1-associated cytokines such as IL-2, IL-12, tumor necrosis factor α (TNF-α) and IFN-γ, remain within the normal ranges across all severity categories (Johnston et al., 2015). These findings suggest the occurrence of cytokine storms and a complex interplay between cytokine signaling pathways and immunomodulatory processes during MPXV infection. Complement-related proteins exhibit an early increase in macaque lung fluid during MPXV infection (Brown et al., 2010). Gene transcription analysis suggest that MPXV infection induces expression of a set of genes that promote nuclear factor-κB (NF-κB) activation (Bourquain et al., 2013). A prediction of genome-wide protein-protein interactions between MPXV and the human proteome shows a high enrichment of immune activation-related proteins (Kataria et al., 2023). These findings add a valuable piece to the puzzle of host immunity against MPXV infection.

Rhesus macaques (RM) develop a robust and sustained adaptive immune response following MPXV infection, accompanied by significant viral replication in the peripheral blood and lungs (Estep et al., 2011).

This response includes an increase in proliferating memory B cells in peripheral blood mononuclear cells and a strong development of orthopox-specific immunoglobulin G (IgG) response (Estep et al., 2011). Notably, both the central memory and effector memory T cells are rapidly increased during the early phase of infection, followed by a dramatic decline (Estep et al., 2011). However, most T-cell subsets then undergo a renewed proliferative phase, characterized by a more sustained elevation (Estep et al., 2011). Additionally, MPXV-specific antibodies, such as IgG and IgM, are extensively detected in MPXV-infected patients and serve as the markers for mpox diagnosis (Colavita et al., 2023). Studies of non-human primates demonstrate that B cells but not $CD4^+$ or $CD8^+$ T cells are essential for vaccine-induced protection against MPXV infection, which highlights the importance of antibody response in MPXV clearance (Edghill-Smith et al., 2005). T cells are also likely to make a significant contribution to overall protective response against MPXV. MPXV-reactive T cells are observed in many healthy individuals, particularly those born before 1976 who likely received smallpox vaccination. Furthermore, vaccination against smallpox induces a group of long-lasting resting memory T cells which are capable of cross-reactivation with MPXV (Adamo et al., 2023).

2.2. Immune evasion

One of the unique property of poxviruses is that they replicate exclusively within the cytoplasm of infected cells (Moss, 2013). As a result, they have evolved multiple immunomodulators that disrupt host antiviral responses through diverse strategies. Here, we discuss some of the immune escape strategies employed by MPXV during infection. The immune evasion by MPXV is summarized in Fig. 2.

2.3. Preventing production of IFNs

Upon infection, cellular pattern recognition receptors (PRRs) sense the conserved components of the invading viruses called pathogen-associated molecular patterns (PAMPs), such as viral genomic DNA. This recognition triggers intracellular signaling cascades that activate key transcription factors, such as interferon regulatory factor 3 (IRF3) and NF-κB, leading to transcriptional induction of antiviral genes and initiation of antiviral innate immune response (Hu and Shu, 2018, 2020; Mogensen, 2009). Several DNA receptors, including cyclic GMP-AMP synthase (cGAS) and DNA-dependent protein kinase (DNA-PK) have been implicated in detecting poxviruses.

One crucial mechanism by which poxviruses evade host immunity is by targeting the cGAS-STING/MITA pathway. cGAS is an ubiquitious cytoplasmic DNA sensor (Li et al., 2013) that detects cytosolic DNA and then catalyzes the synthesis of 2′3′cyclic GMP-AMP (cGAMP) to activate the ER-associted adaptor protein STING (also named MITA). The activated STING/MITA translocates from the ER to Golgi and further to perinuclear punctate structures. These processes result in activation of the transcription factors NF-κB and IRFs as well as transcriptional induction of antiviral genes (Balka et al., 2020; Xia et al., 2019; Zhang & Zhong, 2022; Zheng et al., 2022; Zhong et al., 2008). Poxvirus protein

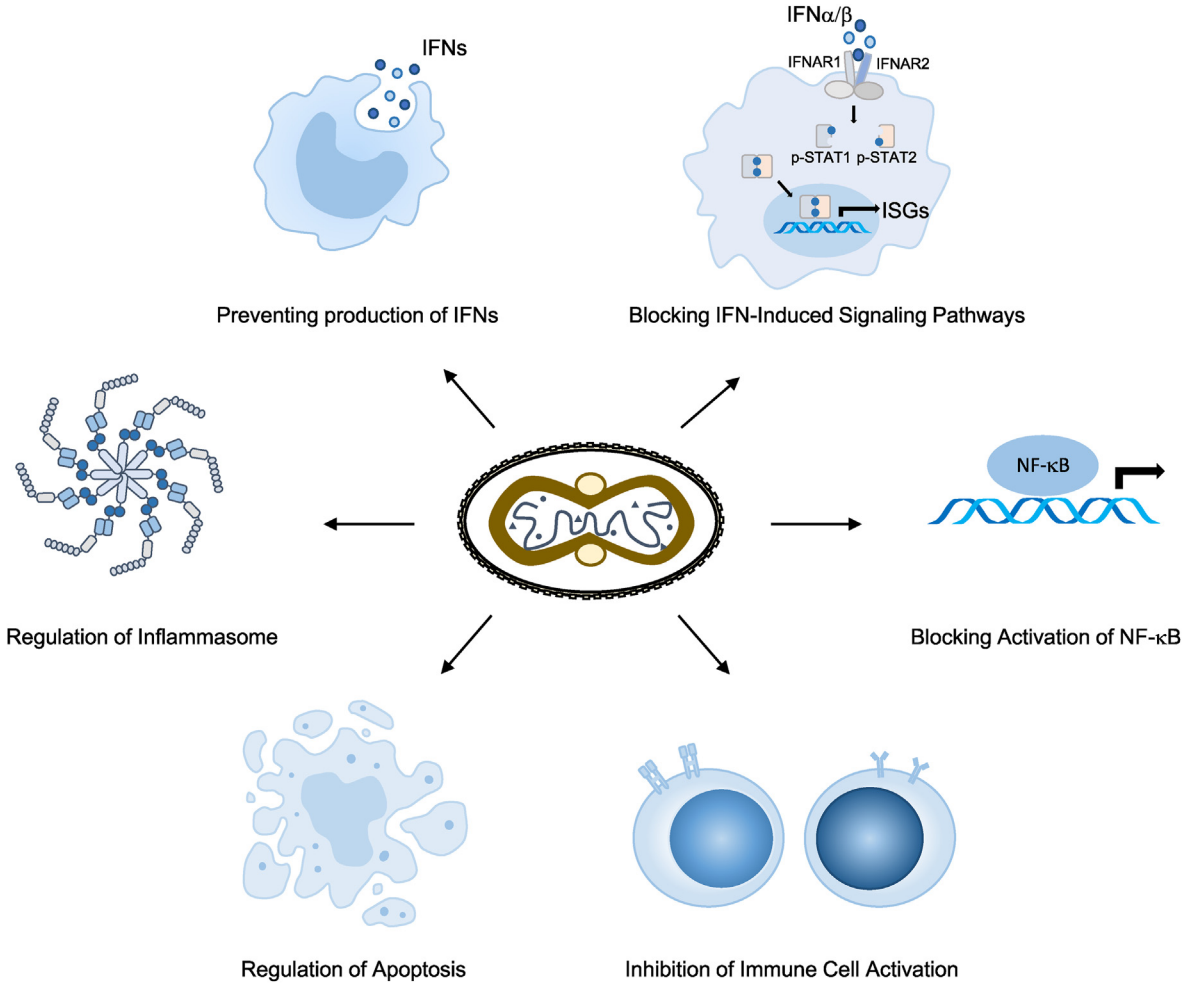

Fig. 2. Immune evasion by MPXV
MPXV encodes multiple immunomodulators that disrupt host antiviral responses through diverse strategies, including preventing production of IFNs, blocking IFN-induced signaling pathways and activation of NF-κB, inhibition of immune cell activation, regulation of apoptosis and inflammasomes. See text for details.

F17, conserved across most poxviruses including MPXV, disrupts cGAS-STING/MITA signaling by sequestering Raptor and Rictor, regulatory factors of mammalian target of rapamycin (mTOR). This sequestration of mTOR results in its excess accumulation in the Golgi apparatus and subsequent mTOR-dependent degradation of cGAS (Meade et al., 2018). Poxviruses employ a family of enzymes known as poxvirus immune nucleases (poxins) which cleave 2′3′-cGAMP to restrict cGAS-STING/MITA signaling. Deletion of the poxin gene (*B2R*) attenuates replication of VACV-WR (Western Reserve strain) *in vivo* (Eaglesham et al., 2019). Poxin is highly conserved in most orthopoxvirus, including MPXV, CPXV, and ectromelia virus (ECTV), but is notably inactivated in VARV and VACV-MVA (Eaglesham et al., 2019). The poxin domain is fused to a Schlafen (Slfn) family-related domain that shares significant similarity to human schlafen proteins, which are regulated by IFNs and initially implicated in T cell quiescence (Hernaez et al., 2020; Mavrommatis et al., 2013). ECTV lacking the viral Schlafen (v-Slfn) shows significantly reduced replication in mouse infection models, accompanied by a robust IFN response (Hernaez et al., 2020). It has also been reported that VACV protein E5 targets cGAS to suppress DNA sensing (Yang, Wang, Dai, et al., 2023).

Poxviruses also target other DNA sensing pathways. VACV proteins C16 and C4, which are conserved in MPXV, interact with Ku and block the binding of DNA to DNA-PK, resulting in inhibition of the DNA-PK-mediated DNA sensing pathway (Peters et al., 2013; Rivera-Calzada et al., 2022; Scutts et al., 2018). Poxviruses encode multiple B cell lymphoma 2 (Bcl-2)-like proteins to interfere the functions of multiple cofactors, leading to inhibition of NF-κB and IRF3 in the innate immune sensing pathways. Poxvirus antagonists, such as VACV-C6, N1, N2 and K7 proteins, belong to a well-conserved group of Bcl-2-like proteins across orthopoxviruses. C6 binds host TANK-binding kinase 1 (TBK-1) adaptor proteins SINTBAD and NAP1, thereby effectively inhibiting the phosphorylation and activation of IRF3 and IRF7, as well as induction of type I IFNs (Unterholzner et al., 2011). It has been shown that tripartite motif protein 5α (TRIM5α) activates NF-κB via synthesis of poly-ubiquitin chain and acts as a restriction factor for orthopoxviruses. C6 binds to and degrades TRIM5α, preventing TRIM5α-mediated NF-κB activation (Zhao et al., 2023). N1 has been demonstrated to suppress IRF3 activation and the induction of downstream genes in MVA-infected cDCs (Dai et al., 2014). N2, an early nuclear protein, is a nuclear IRF3 inhibitor and promotes virulence (Ferguson et al., 2013). VACV protein K7 binds directly to Spir1 to suppress IRF3 activation (Torres et al., 2022).

2.4. Blocking IFN-induced signaling pathways

In addition to restricting interferon production by infected cells, poxviruses develop several strategies to inhibit IFN-induced signaling pathways. VACV encodes a soluble protein called B18, which functions as a decoy receptor for IFN-α but not IFN-β. By binding to IFN-α, B18 inhibits the interaction between IFN-α and its natural receptor, thus abrogating IFN-α signaling (Symons et al., 1995; Waibler et al., 2009). Type II IFN is also neutralized by VACV-encoded protein B8, a soluble decoy receptor that binds IFN-γ extracellularly and inhibits IFN-γ-induced signaling (Alcami and Smith, 1995, 2002). B18 and B8 are both well-conserved across poxviruses, including MPXV, and contribute to virulence (Symons et al., 1995, 2002), suggesting their critical roles in poxvirus pathogenesis. STATs-mediated induction of IFN-stimulated genes (ISGs) is a crucial antiviral defense mechanism employed by hosts. VH1, a virion-associated phosphatase conserved in poxviruses, dephosphorylates STAT1 and STAT2, resulting in inhibition of IFN-triggered signaling and antiviral effects (Mann et al., 2008; Najarro et al., 2001). VACV early protein C6 interacts with STAT2 and HDAC4 to suppress type I IFN response (Lu et al., 2019; Stuart et al., 2016). VACV protein 018, a well-conserved protein across almost all poxviruses, directly binds to the SH2 domain of STAT1 and prevents its recruitment to the phosphorylated IFN-γ receptor 1 (IFNGR1), thereby inhibiting IFN signaling. Consistently, VACV lacking 018 shows reduced virulence and induces enhanced innate immune response in mice (Talbot-Cooper et al., 2022).

Poxviruses also encode proteins that inhibit IFN-induced expression of downstream antiviral genes. For example, poxviruses target protein kinase R (PKR), which is a dsRNA-dependent kinase with multifaceted roles in antiviral defense of the host (Garcia et al., 2006; Munir & Berg, 2013). PKR can activate the NF-κB signaling pathways, promote the production of antiviral cytokines, induce apoptosis of infected cells, and inhibit viral replication by phosphorylating the alpha subunit of eukaryotic translational initiation factor 2 (eIF2α). Poxviruses possess multiple mechanisms to antagonize the PKR pathways for evasion of host defense (Der & Lau, 1995; McAllister et al., 2012; Zamanian-Daryoush et al., 2000). For example, VACV E3 protein, encoded by the *E3L* gene, utilizes its C-terminal dsRNA binding domain to bind dsRNA, which prevents the dimerization and activation of PKR (Chang et al., 1992; Romano et al., 1998). VACV lacking E3 displays a replication defect in HeLa cells. VACV-E3Δ37N, a strain encoding a truncated E3 protein lacking the 37 N-terminal amino acids, exhibits a 100-to 1000-fold reduction in pathogenicity compared to wild-type VACV. Infection with VACV-E3Δ37N triggers activation of the host's antiviral PKR pathway (Arndt et al., 2015; Brandt et al., 2005). MPXV F3 protein, a homologue of VACV E3, lacks 37 amino acids at its N-terminus. However, phenotypically, MPXV resembles wild-type VACV rather than VACV-E3Δ37N. This suggests that MPXV exists compensatory mechanisms to mitigate the partial inactivation of its F3 (Arndt et al., 2015). The ubiquitin-like modifier ISG15, an early antiviral protein, is one of the most prevalent type I IFN-induced proteins. VACV E3 protein binds ISG15 via its C-terminal domain and suppresses its antiviral function (Guerra et al., 2008).

2.5. Blocking activation of NF-κB

NF-κB is a pivotal transcription factor in inflammatory response activated by a wide range of stimuli, including proinflammatory cytokines, and diverse ligands of PRRs. The classical NF-κB pathway involves the activation of IκB kinase (IKK), which phosphorylates and degrades IκBα, an inhibitory protein that sequesters NF-κB in the cytoplasm. Following its liberation from IκBα, NF-κB translocates into the nucleus to induce transcription of the effector genes (Brady & Bowie, 2014; Zhang et al., 2017).

Orthopoxviruses utilize various strategies to antagonize NF-κB activation for immune evasion. Orthopoxviruses encode an IL-1-binding protein (IL-1BP), which binds IL-1β extracellularly and prevents its interaction with IL-1 receptors on the cell surface, thereby inhibiting NF-κB activation (Alcami & Smith, 1996; Spriggs et al., 1992). Orthopoxviruses also encode a soluble IL-18-binding protein (IL-18BP), which is homologous with host IL-18BP, to suppress IL-18-induced activation of NF-κB, leading to reduced IFN-γ production and impaired activation of NK cells and T cells (Born et al., 2000; Reading & Smith, 2003). Numerous orthopoxvirial proteins directly interact with NF-κB signaling components to prevent NF-κB activation. For example, F14, which is conserved among orthopoxviruses, mimics the transactivation domain of NF-κB subunit p65 and inhibits transcription of NF-κB-regulated genes by blocking the association between p65 and NF-κB co-activator CREB--binding protein (CBP) (Albarnaz et al., 2022). VACV encodes several NF-κB inhibitors, such as ankyrin-like proteins B14, A46, A52, A49 and BTB-Kelch proteins A55, C2 and F3. B14 interacts with IKKβ to inhibit its activation and consequently NF-κB activation (Graham et al., 2008; Tang et al., 2018). A46 and A52 are conserved in amino acid sequence with the Toll/IL-1 receptor (TIR) domain of the IL-1/Toll-like receptor (TLR) superfamily. A46 interacts with the TIR-containing adaptor proteins MyD88, MAL/TIRAP, TRAM, and TRIF and impair the signaling triggered by the TLR family members (Stack & Bowie, 2012). A52 blocks TLR-mediated activation of NF-κB by associating with two key proteins, interleukin 1 receptor-associated kinase 2 (IRAK2) and tumor necrosis factor receptor-associated factor 6 (TRAF6) (Harte et al., 2003). A49, a small intracellular protein, contains a motif that closely resembles a

region within IκBα. This motif typically signals IκBα's destruction through its phosphorylation by IKKβ and subsequent binding to the E3 ligase β-TrCP. A49 utilizes this motif to interact with β-TrCP, effectively shielding IκBα from degradation (Mansur et al., 2013). BTB-Kelch proteins A55, C2 and F3 block NF-κB signaling by inhibting nuclear translocation of p65 (Pallett et al., 2019; Zhang et al., 2022).

2.6. Inhibition of immune cell activation

T and NK cells express activating and inhibitory receptors that specifically bind to various members of the major histocompatibility complex class I superfamily (MHCISF). Orthopoxviruses evade T cell- and NK cell-mediated immunologic cytotoxicity by interfering with the functions of these receptors. Natural killer group 2D (NKG2D) is an activating immune receptor expressed by effector T and NK cells. Orthopoxvirus MHC class I-like protein (OMCP), a secreted protein encoded by MPXV and CPXV, binds to NKG2D with high affinity, leading to the inhibition of NKG2D-dependent killing by NK cells (Campbell et al., 2007). The conserved MPXV M2 protein interacts with human B7.1 and B7.2, effectively preventing the binding of CD28 and CTLA4 to their respective human B7.1/2 ligands, thereby hindering T cell activation and proliferation (Kleinpeter et al., 2019; Wang et al., 2019; Yang, Wang, Yu, et al., 2023). In addition, MPXV evades antiviral responses from $CD4^+$ and $CD8^+$ T cells by preventing T cell receptor (TCR)-mediated T cell activation through presentation of alternative antigens (Hammarlund et al., 2008). VACV protein A35, encoded by the *A35R* gene (VACV-Cop designation), is a highly conserved protein among orthopoxviruses, including MPXV. It inhibits MHC class II-restricted antigen presentation, T cell priming and cytokine/chemokine production (Rehm et al., 2010). Orthopoxviruses also encode a soluble IL-18BP to antagonize IL-18-induced inflammation and NK cytotoxicity (Okamura et al., 1998; Reading & Smith, 2003).

2.7. Regulation of apoptosis

Apoptosis, a programmed cell death pathway primarily mediated by caspases, serves as an important mechanism for elimination of virus-infected cells. Orthopoxviruses evolve various strategies to regulate apoptosis for evasion of host defense. The orthopoxvirus-encoded Cytokine response modifying protein A (CrmA), a homologure of serine proteinase inhibitor 2 (SPI-2), suppresses apoptosis by inhibiting caspases 1 and caspases 8 (Macen et al., 1998; Miura et al., 1993; Qin et al., 2017; Srinivasula et al., 1996). VACV encodes the Bcl-2-like proteins F1 and N1, which are highly conserved in MPXV. VACV F1 localizes to mitochondria and functions as a caspase 9 inhibitor, thereby inhibiting the death of infected cells (Taylor et al., 2006; Zhai et al., 2010). VACV N1 harbors a specialized surface groove that enables its interaction with pro-apoptotic Bcl-2 proteins Bid and Bad, ultimately inhibiting apoptosis (Maluquer de Motes et al., 2011).

TNF is not only a potent pro-inflammatory and antiviral cytokine but also plays a pivotal role in apoptosis (Van Antwerp et al., 1998). Orthopoxviruses encode secreted decoy TNF receptors (sTNFRs), which competitively bind to TNF and impair TNF-triggered inflammatory response and apoptosis (Alvarez-de Miranda et al., 2021). There are several orthopoxviral sTNFRs, such as CrmB, CrmC, CrmD, CrmE, and vCD30. Interestingly, MPXV only encodes CrmB (Hu et al., 1994; Suraweera et al., 2020), suggesting a possible difference in its immune modulation strategy compared to other orthopoxviruses.

2.8. Regulation of inflammasomes

Inflammasomes, which are signaling complexes that orchestrate pro-inflammatory cytokine production and trigger pyroptosis, play a pivotal role in antiviral immunity (Boys et al., 2023). The assembly of inflammasomes results in caspase-1 activation, which facilitates the maturation and release of IL-1β and IL-18. The activated caspases also cleave gasdermin-D (GSDMD) to produce a pore-forming fragment, resulting in pyroptosis (Shi et al., 2015).

VACV encodes two proteins, B13 and F1, which are conserved in orthopoxviruses and orthologs of SPI-2, to target components of inflammasomes to overcome host defense. B13 acts as a substrate mimic to inhibit caspase-1 activity, blocking proteolytic processing of IL-1β (Yu et al., 2021). F1 suppresses NLR-mediated IL-1β production and contributes to the virulence of VACV by interacting with and inhibiting NLRP1 (Gerlic et al., 2013). Orthopoxviruses encode secreted viral IL-1β receptors and viral IL-18 binding proteins that effectively prevent IL-1β and IL-18 from binding to their respective cellular receptors (Alcami & Smith, 1996; Born et al., 2000; Spriggs et al., 1992). Although AIM2 inflammasome has been linked to the response to poxvirus infection, currently no poxvirus inhibitors directly targeting AIM2 are identified.

3. Diseases and intervention

3.1. Diseases

Person-to-person transmission of MPXV primarily occurs through respiratory droplets, sexual activities, and close contact with exudates of skin lesions or their contaminants (Beer & Rao, 2019; Palich et al., 2023). Mpox is generally self-limiting, with clade-dependent case fatality rates ranging from 1% to 10%. Two distinct clades of MPXV are of significant clinical importance. Clade I infections are characterized by more severe disease manifestations and a mortality rate approximately three times higher than those caused by clade II (Americo et al., 2023; Bunge et al., 2022).

Infection with MPXV typically begins with fever, muscle aches, and a sore throat. Skin lesions appear approximately 1–3 days following the onset of fever (Dashraath et al., 2022). These lesions are the most common symptoms, often appearing on the face and extremities and causing mild itching or pain. However, the 2022 outbreak, predominantly caused by the Clade IIb virus, has been associated with a higher incidence of genital, perianal, and oral lesions in infected individuals, particularly among MSM (Thornhill et al., 2022). These lesions are often accompanied by more severe pain and secondary infection of the skin bacteria (Patel et al., 2022; Thornhill et al., 2022). MPXV infection tends to cause complications such as pneumonia, encephalitis, keratitis, septicemia, gastrointestinal problems, and secondary bacterial infections (Adler et al., 2022; Huhn et al., 2005).

Severe complications and even death have been reported in mpox outbreaks, especially among vulnerable populations such as young children, pregnant women, and immunocompromised individuals (Dashraath et al., 2022; McCollum & Damon, 2014; Ogoina et al., 2020). Previous outbreaks of mpox have shown increased mortality and hospitalization rates among children, even in higher income countries (Vouga et al., 2022). Epidemiological data from past mpox outbreaks in Africa further corroborates this trend, which indicates that a majority of mpox cases occur in children under 10 years of age (Jezek et al., 1986). Patients coinfected with HIV–I develop a more serious disease compared to those without HIV (Ogoina et al., 2020). Vertical transmission of MPXV in pregnant women has been correlated with fetal death and congenital infection (Mbala et al., 2017) as well as a high probability of miscarriage (Cuerel et al., 2022).

3.2. Vaccines

Vaccines developed for smallpox are also effective against mpox. The U.S. Food and Drug Administration (FDA) has approved two vaccines for pre-exposure vaccination against orthopoxviruses, including MPXV: JYNNEOS (also known as Imvanex or Imvamune), a non-replicating smallpox vaccine, and ACAM2000, a live VACV vaccine of the second-generation (Petersen et al., 2016; Rao et al., 2022; Rizk et al., 2022).

The attenuated third-generation smallpox vaccine JYNNEOS, which is based on Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) strain,

has been safely tested in individuals with immunocompromising conditions (Petersen et al., 2015; Rao et al., 2022). Recommended for active immunization against mpox disease in individuals of all ages, the JYNNEOS vaccine is associated with mild side effects (Meo et al., 2022). A recent study indicates that JYNNEOS vaccination triggers moderate B cell and antibody responses and a more robust T cell response compared to the robust B and T cell responses induced by MPXV infection (Cohn et al., 2023; Mazzotta et al., 2023).

ACAM2000, a replication-competent VACV vaccine, is recommended for individuals over 18 years of age but contraindicated for use in infants, pregnant women, and individuals with cardiovascular diseases and immunosuppressive conditions (Meo et al., 2022). ACAM2000 is associated with distinct mild side effects (Nalca & Zumbrun, 2010; Petersen et al., 2015) and can cause a cutaneous reaction at the injection site, leading to progressive vaccinia in immunocompromised individuals such as HIV patients (Rizk et al., 2022).

Other vaccines have shown potential to prevent MPXV infection. Individuals infected with MPXV generate humoral immune responses that are comparable to those induced by smallpox vaccination, providing opportunities for vaccine and therapeutic development (Otter et al., 2023). Derived from the VACV Tian Tan (VTT) strain extensively used as a smallpox vaccine in China, the non-replicating VACV Tian Tan (NTV) (Zhao et al., 2020), has been identified as a promising next-generation vaccine for smallpox and mpox (Chu et al., 2023; Li et al., 2024). An mRNA-lipid nanoparticle vaccine encoding four key MPXV surface antigens has demonstrated protective immune responses against MPXV and VACV (Freyn et al., 2023). mRNA vaccines encoding fusion proteins of the extracellular domain of MPXV A35R and full-length M1R protect mice from a lethal dose of VACV challenge (Hou et al., 2023). Multi-valent mRNA vaccines, including MPXVac-097 and vaccines against surface proteins of MPXV enveloped or mature viron, elicit strong immune response and neutralizing activity in mice (Fang et al., 2023; Zhang et al., 2023). Furthermore, a subunit vaccine, designed using structure-guided immunogen designs that incorporate MPXV M1 and A35 antigens, demonstrates superior *in vivo* protection against VACV compared to co-immunization with the two individual antigens. This advantage is likely due to the vaccine's ability to retain the native conformation of epitopes, leading to a stronger A35 and M1-specific antibody response (Wang et al., 2024).

3.3. Therapeutics

Several therapies developed for smallpox can be applied to mpox, but their effectiveness for mpox remains to be clinically established. Tecovirimat (also known as TPOXX or ST-246), a pan-orthopoxvirus inhibitor approved by FDA for the treatment of smallpox, is used to treat hospitalized MPXV-infected patients (Matias et al., 2022; Sherwat et al., 2022). Tecovirimat inhibits VP37 (also named F13 in VACV-Cop strain) thereby blocking the final stages of viral maturation and release from infected cells (Russo et al., 2021). However, long-term treatment of tecovirimat in mpox patients with compromised immune systems has been linked to the emergence of tecovirimat-resistant MPXV strains (Smith et al., 2023). Brincidofovir (also known as BCV or CMX001), an inhibitor of viral DNA polymerase approved by FDA for treatment of smallpox, has shown promising results against mpox in MPXV-infected prairie dog models (Hutson et al., 2021). Brincidofovir is an oral analogue of the intravenous drug Cidofovir, which may offer an improved safety profile by its reduced renal damage compared to Cidofovir (Chittick et al., 2017; Lanier et al., 2010). Vaccinia Immune Globulin (VIG) is approved by the FDA to treat smallpox and certain complications caused by vaccination (Wittek, 2006). While its efficacy against MPXV remains unknown, VIG has been used clinically to treat some serious cases of mpox and has been proposed as a potential treatment option for people with T cell lymphopenia who cannot receive the live mpox vaccination (Al-Musa et al., 2022; Thornhill et al., 2022).

Although existing smallpox vaccines and therapeutics have been approved for use against mpox, there remains an urgent need for MPXV-specific vaccines and drugs, particularly for vulnerable populations like children, pregnant women, and individuals with compromised immune systems. The development of novel vaccines and drugs is of paramount importance to effectively prevent MPXV infection and mitigate the risk of severe illness and mortality.

4. Discussion

The 2022 mpox outbreak in non-endemic regions is the largest outbreak of MPXV seen so far. Its widespread transmission has caused concerns among international health authorities (Cabanillas et al., 2022). Studies of other poxvirus and human immune responses against MPXV infection before or after vaccination have provided some information for the understanding of MPXV-host interaction. However, MPXV-host interplays are not entirely the same as other poxviruses, and many issues remain unsolved.

MPXV employs distinct immune evasion mechanisms with other poxviruses, potentially contributing to its virulence. For example, poxin, conserved across most orthopoxviruses, cleaves 2′3′-cGAMP to restrict cGAS-STING/MITA signaling. The poxin protein of MPXV is fused to a Slfn family-related domain, which is absent in VACV-Cop and VACV-WR strains. This raises a question on the precise function of the Slfn family-associated domain in MPXV poxin during virus-host interaction. It would be interesting to investigate whether the Slfn family-associated domain of MPXV poxin plays a role in immune escape. Another example is that the N-terminus of MPXV F3 protein lacks 37 amino acids compared to its homologue, VACV E3 protein. MPXV exhibits similar characteristics to wild-type VACV, but not the VACV strain lacking the 37 N-terminal residues (VACV-E3Δ37N). This suggests MPXV has evolved compensatory mechanisms to mitigate the partial dysfunction of its F3, reflecting its adaptations to host defense. Understanding these mechanisms is essential for deciphering MPXV's unique strategies to interact with the host and gaining insights into its pathogenesis.

The two clades of MPXV also exhibit distinct mechanisms in regulating host defense. MPXV inhibitor of complement enzymes (MOPICE), specifically expressed in Clade I and absent in Clade II, modulates antiviral immune responses by inhibiting complement activation, potentially contributing to the observed increased virulence of Clade I (Chen et al., 2005; Estep et al., 2011; Liszewski et al., 2006). The Clade I MPXV contains a full-length BR-203 virulence factor, whereas the Clade II MPXV only has a truncated version of BR-203, which is correlated with their abilities to impair apoptosis of host cells (Gong et al., 2022; Kindrachuk et al., 2012; Weaver & Isaacs, 2008). These observations suggest that distinct mechanisms may contribute to the different virulence of the Clade I and II MPXV. Future studies are urgently needed for further understanding of MPXV-host interaction, evolution of the virus and mpox pathogenesis, which would be critically important for developing effective antiviral strategies and vaccines.

CRediT authorship contribution statement

Xue-Mei Yi: Writing – original draft, Funding acquisition, Formal analysis, Conceptualization. **Ya-Li Lei:** Writing – original draft. **Mi Li:** Writing – original draft, Funding acquisition. **Li Zhong:** Writing – review & editing. **Shu Li:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

Acknowledgements

The work in the author's laboratory was supported by grants from the National Key R&D Program of China (2023YFC2306100), the National

Natural Science Foundation of China (32200713), the Major Project of Guangzhou National Laboratory (GZNL2024A01014), the CAMS Innovation Fund for Medical Sciences (2019-I2M-5–071), the Major Scientific and Technological Project of Hubei Province (2022ACA005) and the Fundamental Research Funds for the Central Universities (2042023kf0175, 2042022dx0003).

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