

## Review

# The unique immune evasion mechanisms of the mpox virus and their implication for developing new vaccines and immunotherapies

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## ABSTRACT

Mpox is an infectious and contagious zoonotic disease caused by the mpox virus (MPXV), which belongs to the genus *Orthopoxvirus*. Since 2022, MPXV has posed a significant threat to global public health. The emergence of thousands of cases across the Western Hemisphere prompted the World Health Organization to declare an emergency. The extensive coevolutionary history of poxviruses with humans has enabled these viruses to develop sophisticated mechanisms to counter the human immune system. Specifically, MPXV employs unique immune evasion strategies against a wide range of immunological elements, presenting a considerable challenge for treatment, especially following the discontinuation of routine smallpox vaccination among the general population. In this review, we start by discussing the entry of the mpox virus and the onset of early infection, followed by an introduction to the mechanisms by which the mpox virus can evade the innate and adaptive immune responses. Two caspase-1 inhibitory proteins and a PKR escape-related protein have been identified as phylogenomic hubs involved in modulating the immune environment during the MPXV infection. With respect to adaptive immunity, mpox viruses exhibit unique and exceptional T-cell inhibition capabilities, thereby comprehensively remodeling the host immune environment. The viral envelope also poses challenges for the neutralizing effects of antibodies and the complement system. The unique immune evasion mechanisms employed by MPXV make novel multi-epitope and nucleic acid-based vaccines highly promising research directions worth investigating. Finally, we briefly discuss the impact of MPXV infection on immunosuppressed patients and the current status of MPXV vaccine development. This review may provide valuable information for the development of new immunological treatments for mpox.

## 1. Introduction

The mpox virus, previously known as monkeypox virus (MPXV), belongs to the genus *Orthopoxvirus* (OPV) within the family *Poxviridae*. OPVs possess large, double-stranded DNA genomes and can infect a wide range of hosts, from insects and fish to mammals. They often cross species boundaries, leading to zoonotic diseases (Sarker et al., 2019; Molteni et al., 2022). The first zoonotic case of human mpox was reported in the Democratic Republic of the Congo in 1970. Subsequent research identified the virus, which was previously found in monkeys in a Danish laboratory, as the causative agent (Brown and Leggat, 2016; Abdelaal et al., 2022). Although the definitive natural host of MPXV remains uncertain, researchers tend to consider rodents as the primary candidate reservoir, despite the name of the virus (Doty et al., 2017; Hraib et al., 2022).

Historically, MPXV infections have spread across Africa, and MPXV has diverged into Clades I (Congo Basin or Central African Clade) and II (West African Clade), each of which contains several lineages and mutations, as confirmed by genomic sequencing (Bunge et al., 2022). Initially confined to rainforest regions, MPXV did not raise great concerns until the early 21st century. Outbreaks outside of Africa, particularly in the United States Midwest in 2003, marked a shift in global attention (Reed et al., 2004).

The situation escalated further in 2022, leading to an unprecedented pandemic primarily affecting the Western Hemisphere. According to the latest report by the World Health Organization (WHO) in December 2023, there were 92,783 laboratory-confirmed cases in 116 countries, prompting the WHO to emphasize the urgency of addressing mpox (WHO, 2023). Although the WHO lifted the status of a “public

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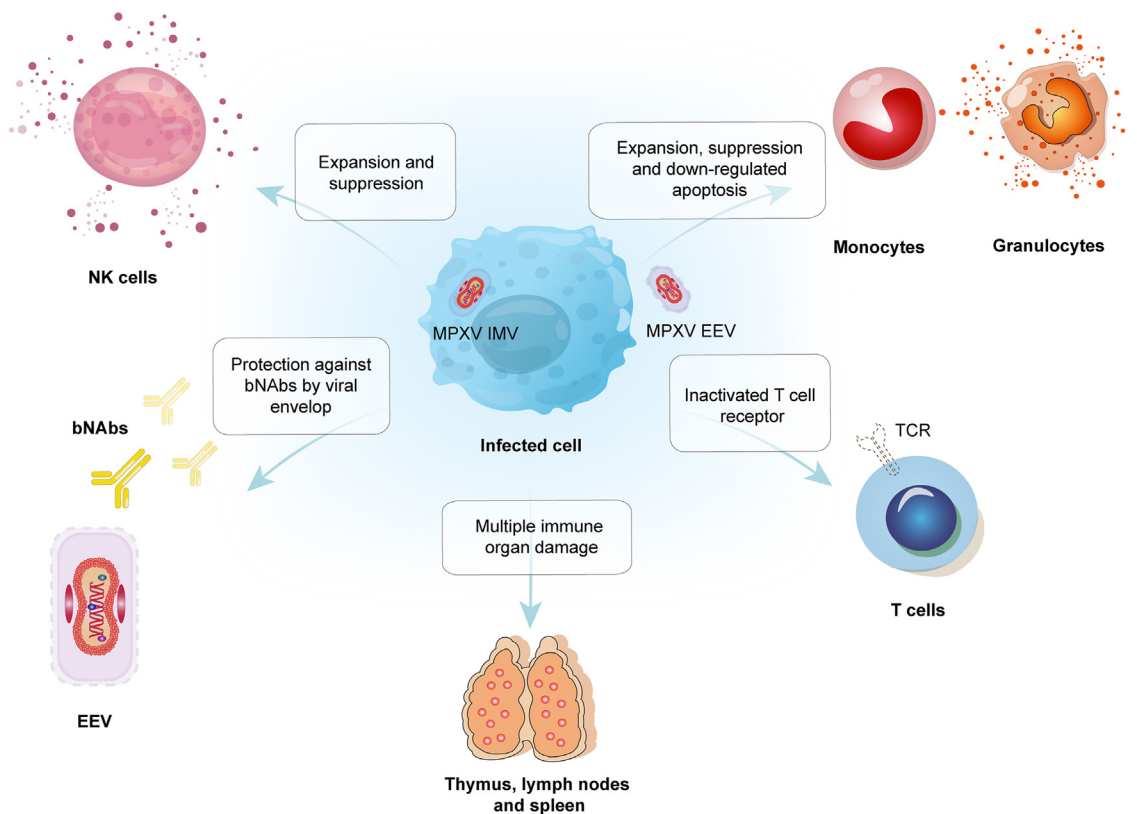
health emergency” for mpox in May 2023, as there has been a gradual decline in newly reported cases worldwide, the threat posed by mpox has not completely subsided. There is still a troubling rise in newly diagnosed cases in Asia. Studies have warned of the potential resurgence of mpox on the continent. From June to November 2023 alone, there were 1,610 newly diagnosed cases in China, compared to about 500 cases reported before June 2023. With some of the most densely populated areas in the world, Asia faces a potential new phase of the mpox pandemic, particularly among men who have sex with men (MSM) populations, with current epidemiological models predicting thousands of new cases if proper precautions are not taken. Potential neglect of prevention measures in some Southeast Asian countries also poses a major challenge to the overall control of mpox (China CDC, 2023; Gong et al., 2022; Endo et al., 2023; Islam et al., 2023; Akhmetzhanov and Wu, 2024; Ma et al., 2024). Controlling these outbreaks will require the development of preventive and therapeutic strategies. Currently, numerous studies on MPXV utilize vaccinia virus (VACV) models or involve cross-species studies among poxviruses, with MPXV often taking a backseat. Our concern is that the distinctive mechanisms allowing MPXV to evade the immune response and its exceptional adaptation in human hosts may have been overlooked. Understanding these unique immune responses to MPXV and its immune evasion strategies in humans is pivotal and forms the core focus of this article.

## 2. Immunopathology of the MPXV

Poxviruses, which are large DNA viruses, differ from smaller viruses in their strategies to overcome immunological barriers. While smaller

viruses rely on rapid replication and exploit their size for efficient host spreading, poxviruses employ intricate, multilayered strategies to promote their survival. However, these sophisticated tactics often trigger more robust immunological responses from the host (Li et al., 2023) (Fig. 1).

Granulocytes and monocytes play crucial roles in the early stages of MPXV infection and replication, as they are among the first lines of defense in innate immunity as well as the primary vectors for the spread of MPXV. After vaccination, granulocytes and monocytes are quickly recruited to the infection site. Upon subsequent immunization, these trained cells can rapidly activate and mature, providing nonspecific protection against poxviruses and other unrelated pathogens (Feraoun et al., 2021). Furthermore, some CCR2<sup>+</sup> inflammatory monocytes can respond to stimulator of interferon genes (STING)-mediated DNA sensing in type II alveolar epithelial cells and subsequently differentiate into macrophages, which effectively block airborne transmission by inhibiting viral replication in the lungs through the engulfment of viral particles (Yang et al., 2022). Additionally, the ratio of granulocytes to lymphocytes may serve as an indicator of immunological outcomes of viral infection (Dyall et al., 2017; Li et al., 2020). Moreover, elevated blood monocyte and granulocyte cell counts have been noted in human patients, while animal studies have shown a significant rise in monocyte cell count and activity following a general decline in both innate and adaptive immune cells (Anderson et al., 2003; Huhn et al., 2005). Notably, the Congo Basin MPXV strain behaves differently in monocytes. It can selectively modulate host cell signaling through unique phosphorylated kinases, leading to significant lower levels of monocyte apoptosis compared to



**Fig. 1.** The immune response following MPXV infection and the immune evasion strategies employed by MPXV. Briefly, MPXV triggers widespread expansion of both innate and adaptive immune cells. In the initial stages post-infection, the proliferation of monocytes, granulocytes, and NK cells is significantly increased. Moreover, MPXV employs multiple strategies to evade the host immune response. It suppresses the activation of monocytes, granulocytes, and natural killer (NK) cells, inhibiting their apoptosis and allowing them to be used as vectors for their spread. Additionally, MPXV can inactivate the TCR on CD4<sup>+</sup> and CD8<sup>+</sup> T cells, hindering their activation. Furthermore, it integrates host-cell membrane proteins to shield itself from neutralizing antibodies. This process also causes damage to multiple immune organs. MPXV: Mpox virus; NK cells: natural killer cells; IMV, intracellular mature virion; EEV: extracellular enveloped virion; TCR: T-cell receptor; bNAbs: broadly neutralizing antibodies.

infection with the West African strain of MPXV or VACV (Table 1) (Kindrachuk et al., 2012; Silva Gomes et al., 2012).

Another crucial innate immune cell type affected by MPXV is natural killer (NK) cells. These cells are actively mediated by multiple enzymes and pathways (Oberlies et al., 2009; Minculescu et al., 2021). Accumulating evidence indicates significant expansion of NK cells in response to MPXV infection, coupled with systematic suppression of NK cell function by MPXV (Song et al., 2013).

CD4<sup>+</sup> and CD8<sup>+</sup> T cells are also rendered inactive by MPXV, thus facilitating the effective spread of the virus via cell-associated viremia. In combination with its ability to disseminate through circulating monocytes, MPXV can evade attacks from virus-specific neutralizing antibodies (NAbs) (Hammarlund et al., 2008). Moreover, the immunopathology of MPXV is not limited to the cellular level. MPXV can cause severe inflammatory reactions and hypertyrosinemia and, in severe cases, damage multiple immune organs, such as the thymus, lymph nodes and spleen (Tang et al., 2023).

### 3. Innate immune responses to the MPXV and immune evasion

#### 3.1. DNA sensing

DNA sensors are essential for detecting intracellular viral genomes. Factors such as cyclic GMP-AMP synthase (cGAS), DNA-dependent protein kinase (DNA-PK), and interferon- $\gamma$  inducible protein 16 (IFI-16) play roles in this recognition process. Many viral DNA sensors function as mediators of nuclear DNA damage repair. After the recognition of viral DNA, these sensors can activate the production of multiple cytokines and trigger autophagy and other proinflammatory responses (Dunphy et al., 2018; Gui et al., 2019; Lu and Zhang, 2020). The vital role of DNA sensors in defending against viral infection also designates them as important targets for MPXV immune evasion (Fig. 2).

cGAS, a wide-range cytoplasmic viral DNA sensor, recognizes numerous viruses, including DNA viruses and retroviruses, as well as other microorganisms and tumor cells (Liu et al., 2021; Domizio et al., 2022; Sokac et al., 2022). After recognition of the viral genome, interferon (IFN) expression can be upregulated through the cGAS-STING pathway, which involves STING activation by IFI-16 (Dunphy et al., 2018). This pathway plays an important role in defending against viruses from the family *Poxviridae*, as shown in studies on MPXV vaccination via modified vaccinia Ankara-Bavarian Nordic (MVA-BN) (Dai et al., 2014; Cheng et al., 2018). Additionally, wild-type VACV can disrupt the cGAS-STING-NF- $\kappa$ B pathway by mimicking the transactivation domain of the p65 subunit of NF- $\kappa$ B with the VACV F14 protein encoded by the

VACV F14L gene and selectively inhibit the activation of NF- $\kappa$ B-dependent antiviral genes. The F14 protein is highly conserved among all OPVs. The homologous F14 protein from MPXV shows the highest identity (98.7%) with the F14 protein of VACV. Furthermore, the transcriptional regulatory sequences adjacent to the open reading frames (ORFs) of the F14L gene are highly conserved (Albarnaz et al., 2022). Thus, it is reasonable to believe that MPXV employs mechanisms similar to those of VACV to disrupt the cGAS-STING-NF- $\kappa$ B pathway.

AIM2 is a cytoplasmic DNA sensor that modulates the inflammatory response (Burckstummer et al., 2009). Poxviruses can trigger apoptosis through the activation of caspase-1 and the upregulation of IFN- $\beta$  expression. Caspase-1 is also an indirect target of the orthologs of poxvirus serine proteinase inhibitor 2 (SPI-2) and cytokine response modifier A (CrmA). These viral proteins can effectively abolish the IFN- $\beta$  induction and caspase-1 activation induced by poxvirus infection to prevent cytokine activation and apoptosis (Qin et al., 2017). In contrast, AIM2 can recognize the poxvirus genome and form a caspase-1-activating inflammasome with an apoptosis-associated speck-like protein with a caspase activation and recruitment domain (Hornung et al., 2009). Unlike other DNA sensors, no apparent direct mechanism against AIM2 has been found for MPXV thus far, which makes it an excellent target for developing vaccines against MPXV.

DNA-PK binds to viral DNA released into the cytosol and triggers the transcription of multiple cytokines and chemokines that are either dependent or independent of STING (Ferguson et al., 2012). DNA-PK consists of two parts: a DNA-dependent protein kinase catalytic domain and a Ku heterodimer. The latter is also a major component of the nonhomologous end joining (NHEJ) pathway for dsDNA repair and is capable of recruiting the former to its location. The Ku heterodimer binds and recognizes the viral DNA genome (Yin et al., 2017; Chen et al., 2021). Some poxviruses, such as MPXV, encode the C16 protein, whereas others encode the C4 protein, which shares 54.4% identity and has an overlapping function with C16 proteins. However, each member of a poxvirus encodes at least one of these proteins, and some, such as VACV, encode both. Moreover, evidence has shown that the nonidentical regions of the C4 and C16 proteins are expendable. The C4 and C16 proteins specifically bind to the Ku heterodimer domain on DNA-PK and effectively block its contact with the viral genome. This makes poxviruses experts in antagonizing DNA-PK sensing (Peters et al., 2013; Scutts et al., 2018).

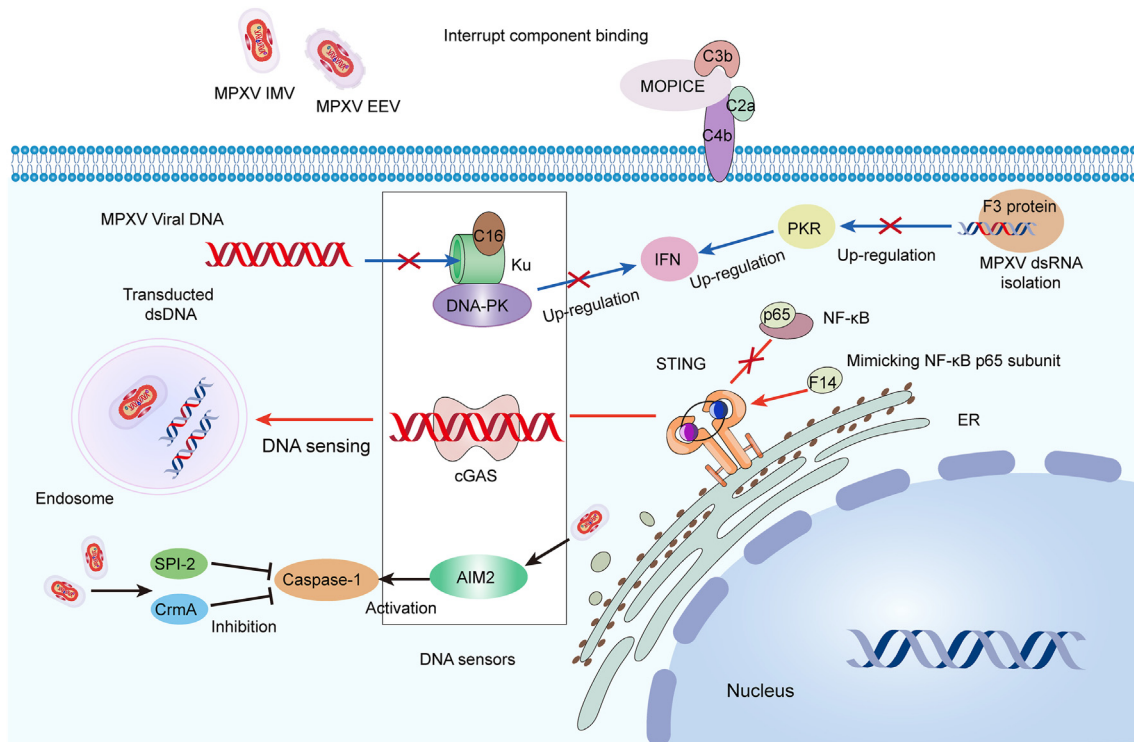
A recent phylogenomic study revealed that the MPXV caspase-1 inhibitor SPI-2 and CrmA and a PKR antagonist called the K3 protein (which we will explain later) act as hubs regulating the interaction between MPXV and the human immune system. Both of these DNA-sensing

**Table 1**

Similarities and differences in the regulation of immune components among Vaccinia virus, Clade I Mpxo virus and Clade II Mpxo virus.

	Vaccinia virus	Clade I Mpxo virus	Clade II Mpxo virus
Blood Monocyte	Increased proliferation	Increased proliferation and reduced apoptosis	Increased proliferation
Natural killer cell	Significant expansion	Significant expansion and suppressed IFN production	Significant expansion and suppressed IFN production
cGAS-STING NF- $\kappa$ B pathway	Mimicking NF- $\kappa$ B p65 subunit with F14 protein	Mimicking NF- $\kappa$ B p65 subunit with F14 protein	Mimicking NF- $\kappa$ B p65 subunit with F14 protein
Caspase-1	Inhibition with SPI-2 and CrmA	Inhibition with SPI-2 and CrmA	Inhibition with SPI-2 and CrmA
DNA-PK	Binding to Ku heterodimer with C4 and C16 protein	Binding to Ku heterodimer with C16 protein	Binding to Ku heterodimer with C16 protein
IFN-PKR pathway	Suppressing PKR with E3 and K3 protein	Suppressing PKR with F3 protein with truncated N-terminal but absent of K3 protein	Suppressing PKR with F3 protein with truncated N-terminal but absent of K3 protein
Complement system	Blocking C3 and C4 component interaction and induce C3 component decay with VCP	Blocking C3 and C4 component interaction with MOPICE	Absence of MOPICE
Cell-mediated immunity	Diminishes peptide loading in MHC-II and interfere with T cell control with B22 protein	Interfere with T cell control using the B22 protein, interrupt CD28 signaling with the M2 protein, and induce nonresponse of the TCR	Interfere with T cell control using the B22 protein, interrupt CD28 signaling with the M2 protein, and induce nonresponse of the TCR

cGAS: cyclic GMP-AMP synthase; STING: Stimulator of interferon genes; SPI-2: Poxvirus serine proteinase inhibitor 2; CrmA: cytokine response modifier A; DNA-PK: DNA-dependent protein kinase; PKR: protein kinase R; VCP: vaccinia virus complement control protein; MOPICE: MPOX inhibitor of complement enzyme.



**Fig. 2.** Immune evasion of DNA sensors and complements by MPXV. MPXV specializes in evading DNA sensing and complement responses. It induces the rapid decay of C3 convertase and encodes MOPICE to prevent the binding of the third and fourth components, disrupting both the classical and alternative complement pathways. Poxviruses produce C4 and/or C16 protein (MPXV only produces C16) which bind to Ku heterodimer, preventing it from recognizing viral genome, recruiting protein kinase catalytic domain and up-regulating IFN; MPXV produces F14 protein to mimic the p65 subunit of NF- $\kappa$ B and inhibits selectively the activation of NF- $\kappa$ B-dependent antiviral genes thus interrupting cGAS-STING pathway; MPXV produces SPI-2 and CrmA to inhibit caspase-1 activation and abolishes IFN- $\beta$  induction thus suppressing apoptosis; MPXV produces F3 protein to bind viral dsRNA and isolates it from PKR to prevent IFN up-regulation. MPXV: Mpx virus; MOPICE: MPOX inhibitor of complement enzyme; dsDNA/RNA: double-strand DNA/RNA; DNA-PK: DNA-dependent protein kinase; PKR: protein kinase R; cGAS: cyclic GMP-AMP synthase; STING: Stimulator of interferon genes; ER: Endoplasmic reticulum; SPI-2: Poxvirus serine proteinase inhibitor 2; CrmA: cytokine response modifier A.

inhibitory proteins is closely related to dozens of human proteins (Kumar et al., 2023). These findings suggest that MPXV has evolved strong tropism for the human host, potentially explaining its exceptional ability to evade the human immune system.

### 3.2. Natural killer cells

The innate immune response to MPXV remains a subject of ongoing study. However, compelling evidence indicates the pivotal role of NK cells in combatting initial MPXV infection. As large granular lymphocytes, NK cells play crucial roles in activating innate immunity and establishing a bridge to adaptive immunity in response to viral infections. Their functions involve direct cytolytic actions against virus-infected cells and the production of key cytokines, such as interferon- $\gamma$  (IFN- $\gamma$ ) and tumor necrosis factor (TNF)- $\alpha$ , which contribute to the inflammatory response (Arase and Lanier, 2004; Freud and Caligiuri, 2006; Quatrini et al., 2021).

Experiments utilizing mouse models have underscored the direct impact of the number and function of NK cells on host susceptibility to poxviruses. For example, the castaneous (CAST) mice, which are characterized by considerably lower NK cell counts than those of other inbred strains, exhibited delayed and reduced TNF- $\alpha$  and IFN- $\gamma$  responses to VACV infection compared with those of BALB/c mice, whereas a lethal intraperitoneal dose of VACV to BALB/c mice led to a markedly greater response than that of CAST mice. Treatment with exogenous IFN- $\gamma$  and TNF- $\alpha$  effectively suppressed VACV replication in CAST mice, thus significantly prolonging survival (Earl et al., 2017, 2020). Additional research suggests that selective reconstitution of the IFN- $\gamma$  gene, specifically in NK cells and not T cells, is sufficient to restore systemic control of VACV in IFN- $\gamma$  OFF mice (Borst et al., 2020).

When CAST and BALB/c mice were infected with MPXV, the outcomes mirrored those following VACV infection. Notably, robust MPXV replication occurred in the lungs of both strains of mice following intranasal infection but only spread to other organs in CAST mice. Moreover, the lethal dose for CAST mice via intraperitoneal injection was approximately 50 times greater than that via intranasal administration.

MPXV inoculation triggers substantial NK cell expansion. However, MPXV hinders the ability of NK cells to secrete IFN- $\gamma$  and TNF- $\alpha$  through unknown mechanisms (Song et al., 2013). Moreover, a mammalian IL-18-binding protein homolog has been identified as being produced by various poxviruses (Xiang and Moss, 1999; Reading and Smith, 2003; Esteban and Buller, 2004). Given that MPXV has a similar effect on NK cells, we propose a similar mechanism by which MPXV inhibits the production of IFN- $\gamma$  and TNF- $\alpha$  by NK cells. These cytokines orchestrate the recruitment of various innate and adaptive immune cells to sites of inflammation by regulating chemokine receptors such as CXCR3, CCR5 and CCR6 (Mohan et al., 2002; Ma et al., 2005; Reeves et al., 2010), potentially explaining the localized organ confinement observed in BALB/c mice. An important implication of these findings is the crucial role played by IFN- $\gamma$  and TNF- $\alpha$  secreted by NK cells in controlling poxvirus replication. Additionally, these cytokines appear to be associated with the spectrum of cross-species/organ tropisms and the adaptation of poxviruses (Americo et al., 2010; Earl et al., 2012; Rahman and McFadden, 2022).

### 3.3. IFN-PKR pathway

Understanding the mechanisms underlying the pathology and pathogenesis of MPXV in human hosts remains a challenge. However, insights from studies of related viruses, particularly members of the genus *Orthopoxvirus*, offer valuable parallels for understanding MPXV.

IFN, which is a pivotal product of NK cells, plays a fundamental role in the host immune response. The functions of IFN span from initiating the innate immune response to orchestrating adaptive immune responses and establishing an antiviral state by activating various IFN-stimulated genes. Essentially, IFN acts as a beacon for the entire antiviral immune response (Samuel, 2001; Ivashkiv and Donlin, 2014). The ability of viruses to evade or suppress the host's IFN response is often a critical determinant of their success in invading the host. OPVs, which are renowned for their resistance to IFN activity, have evolved an important advantage in this respect (Arsenio et al., 2008; Domingo-Gil et al., 2008).

VACV, a prototype member of the family *Poxviridae* that was historically used as a live smallpox vaccine until the eradication of smallpox in 1982, remains the most extensively studied OPV (Perdiguero and Esteban, 2009; Meyer et al., 2020). Early resistance to type-I IFNs, including IFN- $\alpha$  and IFN- $\beta$ , was noted in research conducted in 1973 by Thacore and Youngner, who studied the different IFN-induced resistance pathways of DNA and RNA viruses. The same research further revealed that VACV not only is IFN-resistant but also has some level of capacity to rescue pseudorabies and stomatitis viruses from the IFN response (Thacore and Youngner, 1973). Other studies have demonstrated that VACV encodes an inhibitory factor capable of isolating virus-produced free dsRNA and subsequently impairing the activation of an IFN-inducible dsRNA-dependent pattern recognition receptor called protein kinase R (PKR). PKR is involved in the induction of apoptosis and the inhibition of cell differentiation and proliferation. This discovery eventually led to the purification and identification of the E3 protein, which is a small but potent PKR inhibitor encoded by the VACV *E3L* gene (Akkaraju et al., 1989; Watson et al., 1991; Taga et al., 1999; Tang et al., 2019; Ukhueduan et al., 2021).

Similar to that in VACV, the *F3L* gene in MPXV encodes the F3 protein, which is homologous to the E3 protein of VACV but has a greater capacity to suppress the PKR response. Moreover, MPXV has evolved strategies to minimize the partial inactivation of *F3L* genes by hosts, potentially contributing to its superior virulence against human hosts and significantly reduced susceptibility to certain antipoxvirus drugs compared to VACV and many other OPVs (Arndt et al., 2016; Ando et al., 2020).

The VACV E3 protein consists of an N-terminal region and a C-terminal region, both of which are essential for maintaining its dsRNA affinity and inhibitory function. Truncation of the VACV E3 N-terminus (VACV E3 $\Delta$ 37 N) may result in increased PKR activation (Langland and Jacobs, 2004; White and Jacobs, 2012). Interestingly, unlike the VACV E3 protein and most other E3 protein homologs, the MPXV F3 protein has a truncated N-terminus similar to VACV E3 $\Delta$ 37 N but is able to maintain its function, similar to the wild-type VACV E3 protein. This ability of the MPXV F3 protein to function without its N-terminal segment seems to be extragenetic, as evident from the impairment of VACV replication when its *E3L* gene is replaced with the *F3L* gene of MPXV (Shchelkunov et al., 2001; Arndt et al., 2015). Another possibility is that, since MPXV produces significantly lower levels of dsRNA during intermediate and late transcription than VACV does, the isolation of dsRNA is less critical for the prevention of PKR activation. Additionally, this characteristic may enhance the resistance of MPXV to some antipoxvirus drugs, such as IBT, which relies on prolonging intermediate and late viral transcription (Arndt et al., 2016; Park et al., 2021).

Counteracting PKR is not confined solely to E3 protein homologs among poxviruses. The levels of PKR and other host immunological components vary among species and evolve rapidly and intraspecifically. Many OPVs, including MPXV and VACV, infect a wide range of hosts, thus necessitating the evolution of alternative factors and mechanisms to target specific species (Park et al., 2019).

In addition to the E3 protein, VACV synthesizes other host-range PKR inhibitors, notably the K3 protein encoded by the VACV *K3L* gene (Froggatt et al., 2007). This protein utilizes a distinct mechanism from that of the VACV E3 protein to counteract PKR. However, the rapid evolution of primate PKRs has led to relatively lower susceptibility to

immunological manipulation by the VACV K3 protein (Rothenburg et al., 2009).

Under selective pressures, such as the loss or ineffectiveness of the *E3L* gene, a minor fraction of the VACV population may undergo recurrent duplication of its *K3L* gene, resulting in 'gene-accordions' harboring more than ten copies of the *K3L* gene. This expansion contributes to a 7%–10% increase in the genome and sufficiently upregulates the expression of the VACV K3 protein to overcome host PKR. Furthermore, this duplication provides a platform for rapid mutation to acquire substitutions for the wild-type K3 protein, thereby enhancing the adaptability of the VACV (Elde et al., 2012). A *K3L* ortholog was identified in MPXV; however, its ORFs are interrupted by a premature stop codon (Bratke et al., 2013).

This ongoing evolutionary competition between the evasion mechanisms of poxviruses and their host PKR underscores the dynamic nature of their interaction, thus exemplifying the "Red Queen conflict"—a zero-sum game where every adaptation by host PKR or its evasion mechanisms of poxviruses is met with corresponding adaptations (Brockhurst et al., 2014).

### 3.4. Complement system

The complement system, which is a well-defined and crucial component of both innate and adaptive immunity, plays a vital role in defending against a wide range of pathogens through various pathways. This system responds to multiple immunological processes, such as antibody and lectin binding, as well as the production of inflammatory cytokines (Ling and Murali, 2019). During viral infection, this system recognizes antibodies previously bound to a virus and activates pathways integral for capsid coating and blocking the entry of the virus (Smith and Nemerow, 2019).

VACV encodes two proteins collectively called the vaccinia virus complement control protein (VCP), which derives its name from its structural similarity to the superfamily of complement control proteins (CCPs). VCP induces rapid decay of C3 convertase and binds to the third and fourth complement components, thereby interrupting both the classical and alternative complement pathways (McKenzie et al., 1992; Jha and Kotwal, 2003).

The *D14L* gene encode the MPOX inhibitor of complement enzyme (MOPICE) in the Congo Basin MPXV strain. This enzyme functions as an ortholog of the VCP and operates in a similar manner, although evidence suggests that MOPICE may lack decay-accelerating abilities. Notably, the *D14L* gene is entirely absent from the West African MPXV genome (Liszewski et al., 2006).

The precise role of MOPICE in the differences of virulence between the Congo Basin MPXV and West African MPXV strains remains controversial. In a prairie dog model, the removal of MOPICE resulted in alleviated symptoms and an increased survival rate. However, in a rhesus macaque model, truncation of the *D14L* gene did not decrease the virulence of the Congo Basin MPXV strain; instead, it delayed the adaptive immunity of the host and enhanced viral replication (Estep et al., 2011; Hudson et al., 2012).

These conflicting results were clarified by evaluating the species specificity of the extracellular enveloped form of MPXV. The OPVs exist in two primary forms within the host, namely, the intracellular mature virus (IMV) and the extracellular enveloped virus (EEV). In contrast to EEV, IMV lacks an extracellular envelope; however, both forms of viral MPXV have the capacity to infect human host cells (Su et al., 2022). Compared to IMVs, EEVs are known to be more resistant to complement neutralization, and studies indicate that this resistance is not conferred by any of the tested EEV outer membrane proteins of non-host origin (Smith, 1999). Further investigation revealed that EEVs exhibit resistance to complement neutralization only when they are of cellular origin and are specifically resistant to complements from the same species as other cells are. Additionally, host CCP components are found on the outer membrane of EEVs (Vanderplasschen et al., 1998). This underlying

mechanism could clarify the diverse results obtained from different species in MPXV studies and further support the notion that rodents might be the natural hosts of MPXV.

#### 4. Adaptive immune response and the evasion of MPXV

##### 4.1. Cell-mediated immunity

As the innate immune system swiftly detects and manages pathogens, adaptive immunity offers a more well-tuned recognition system that coordinates intricate collaboration among immune cells to effectively eliminate threats.

The major histocompatibility complex (MHC) plays a pivotal role in defending the adaptive immune system against viral infections. The MHC functions in selecting, differentiating, and activating CD4<sup>+</sup> and CD8<sup>+</sup> T cells. The binding of viral peptide/MHC complexes on antigen-presenting cells to T-cell receptors (TCRs) triggers the activation of T cells, initiating both cellular and humoral immunity (Yin et al., 2012; Szeto et al., 2020). Throughout the extensive coevolutionary history of poxviruses and their hosts, these viruses have developed numerous strategies and mechanisms specifically aimed at either disrupting MHC-TCR recognition or directly preventing T-cell activation.

Cowpox virus (CPXV) employs the CPXV 12 and CPXV 203 proteins to interfere with antigen presentation. CPXV 12 binds to the peptide loading complex, thus obstructing the peptide loading process. Conversely, CPXV 203 sequesters fully loaded peptide-MHC class I (MHC-I) complexes within the endoplasmic reticulum (ER) by manipulating KDEL-mediated ER retention. Like CPXV, the molluscum contagiosum virus confines host MHC-I within the ER by engaging tapasin through its luminal domain. In the case of VACV, it diminishes antigenic peptides and hampers their loading into the MHC, with a primary focus on MHC class II (MHC-II). Targeting VACV-specific peptides via specially designed vectors may restore the activation of antigen-specific CD4<sup>+</sup> T cells (Byun et al., 2009; Rehm et al., 2009; Harvey et al., 2019; Hobbs et al., 2020). In contrast to the majority of poxviruses, MPXV does not manipulate the MHC complex directly. Alternatively, it may induce a state of unresponsiveness in T cells that impacts both MHC presentation and some MHC-independent TCR stimuli (Hammarlund et al., 2008).

MPXV carries the B22 protein, which has been demonstrated to interfere with T-cell control of viral dissemination, although this ability is not entirely exclusive to MPXV, as a few other poxviruses, such as VACV and CPXV, also encode homologous B22 proteins and function in a similar manner (Alzhanova et al., 2014). A recent study revealed that the MPXV M2 protein has a strong affinity for the B7.1 and B7.2 ligands. The oligomeric MPXV M2 protein may disrupt the interaction between B7 ligands and CD28 as well as CTLA4 (Yang et al., 2023). However, since CTLA4 has a much greater affinity for B7 proteins than for CD28 (Pentcheva-Hoang et al., 2004), the MPXV M2 protein likely inhibits the CTLA4 protein less effectively than it inhibits CD28. While CD28 provides a positive signal for T-cell activation, CTLA4 serves as a negative signal for T-cell tolerance and exhaustion. Furthermore, the M2 protein can also increase the stimulation of PD-L1 by B7.1, thus deactivating T cells. Therefore, selectively regulating the costimulation signal of human B7.1/2. MPXV excels in antagonizing human CD4<sup>+</sup>/CD8<sup>+</sup> T cells (Parry et al., 2005; Esensten et al., 2016). This mechanism of MPXV is highly effective, as CD28 is essential for germinal center formation and B-cell maturation, which in turn determines CD4<sup>+</sup>/CD8<sup>+</sup> T-cell activation. The MPXV M2 protein may perpetuate an amplifying loop that impairs the long-term development of adaptive immunity against MPXV (Ferguson et al., 1996; Rastogi et al., 2022). The ability to inhibit T-cell activation endows MPXV with not only immune evasion capabilities but also suppressive tendencies, allowing it to rescue viruses beyond poxviruses. Notably, the production of the M2 protein from MVA-BN is defective, allowing it to induce a more robust immune response than MPXV and wild-type VACV (Kleinpeter et al., 2019). This result indicates that

further removal of other inhibitory genes from MVA may induce stronger CD4<sup>+</sup>/CD8<sup>+</sup> T-cell activation, yielding more effective MPXV vaccines.

##### 4.2. Humoral immunity

While B cells are pivotal in providing protection against viruses post-vaccination, their direct competition with poxviruses is not as pronounced as that of T cells. However, as professional antigen-presenting cells, B cells exhibit increased expression of costimulatory ligands for T-cell coreceptors such as CD28 and ICOS (CD278). As explained earlier, these ligands play critical roles in the expansion and activation of poxvirus-specific CD4<sup>+</sup>/CD8<sup>+</sup> T cells. Moreover, they influence the fate of T follicular helper cells, thereby determining the trajectory of activated B cells (Salek-Ardakani et al., 2009; Linterman and Vinuesa, 2010).

MPXV infection also induces a diverse array of NAbs, including anti-H3, anti-A27, anti-D8, and anti-L1 antibodies to target IMV, or anti-B5 and anti-A33 antibodies to target EEV. However, as mentioned previously, EEVs exhibit high resistance to complement, thereby diminishing the effectiveness of NAbs against the envelopes of EEVs. Research indicates that while NAbs can successfully impede the release of EEVs, their efficacy in completely eliminating EEVs is limited, as complement enhancement plays a crucial role in their neutralizing capacity (Jha and Kotwal, 2003; Gilchuk et al., 2016).

Fortunately, advances in immunoinformatics have provided computational tools with which to predict the outer membrane components of EEVs originating from specific immune cell phenotypes. The novel multi-epitope vaccines designed on the basis of this technology have yielded promising results in animal models (Aiman et al., 2022; Aziz et al., 2022).

#### 5. MPOX in immunosuppressed individuals

Immunosuppression (IS) refers to an impaired immune system resulting from natural diseases or medical procedures that increase susceptibility to various ailments (Ahmed et al., 2023). A recent study in a Beijing cohort revealed that MPXV infection strongly overlapped with HIV and syphilis coinfection. Evaluating the susceptibility of HIV patients to MPXV poses challenges due to the shared transmission routes involving skin and anal lesions in both mpox and HIV/syphilis cases, particularly among MSM. Nevertheless, case studies underscore the importance of screening for HIV infection in MSM patients diagnosed with MPXV infection (Jia et al., 2023, 2024). A global case series revealed that individuals with advanced HIV infection, particularly those with lower CD4<sup>+</sup> T-cell counts, experienced severe mpox symptoms, extensive organ spread, and increased mortality (Mitja et al., 2023). Deficiencies in effector CD8<sup>+</sup> T cells, as evidenced by impaired Ki67, CD25, and T-bet production, also increase the mortality rate of mice infected with VACV (Desai et al., 2018).

Furthermore, IS can potentially compromise the effectiveness of vaccination. In macaques with AIDS, protection from lethal doses of MPXV was not achieved through the smallpox vaccine, likely due to defective immunoglobulin switching (Edghill-Smith et al., 2005). However, a recent study revealed the persistence of anti-MPXV H3L IgG antibodies after MVA-BN administration. This finding indicates that following two doses of the vaccine, antibody titers are similar across groups, including those with a history of smallpox vaccination and individuals infected with HIV, thus highlighting the broad effectiveness of vaccination for patients with compromised immune systems (Kottkamp et al., 2023).

#### 6. Smallpox vaccination-mediated protection against MPXV

Currently, no specific vaccine exists for MPXV. However, due to its close similarity to VACV, smallpox vaccination offers varying degrees of protection against other OPVs, including MPXV. A study in the Democratic Republic of the Congo revealed that approximately 90% of

identified MPXV-infected patients had no prior exposure to OPV infection or smallpox vaccination (Rimoin et al., 2010), suggesting a potential link between recent mpox outbreaks and the eradication of smallpox.

During the 2003 mpox outbreak in the US, the second-generation smallpox vaccine ACAM2000™, which was derived from the monoclonal virus Dryvax, was tested, but the results were suboptimal. Although the vaccine partially alleviated symptoms and improved survival rates, it was ineffective at preventing infection. Furthermore, it is contraindicated in high-risk individuals, such as those with HIV infection. The associated side effects also raise concerns (Brown and Leggat, 2016; Wang et al., 2024). The most recent smallpox vaccine used for mpox is the third-generation smallpox vaccine called MVA-BN, also known as IMVAMUNE or JYNNEOS. This vaccine is primarily intended for emergencies in adults at risk of variola virus (VARV), MPXV, or other poxvirus infections, as well as those at risk of adverse reactions to vaccination. MVA-BN exhibited efficacy in animal tests by significantly increasing cell-mediated and humoral immunity in response to MPXV (Hatch et al., 2013). In human patients, MVA-BN displayed slightly greater protection against MPXV than ACAM2000™. Importantly, MVA-BN poses no contraindications in recipients with immunodeficiency diseases, and no safety issues have been reported (Rao et al., 2022; Ryckeley et al., 2023). Currently, neither of these two vaccines is available for widespread public administration, as further safety testing in human patients is needed.

Recently, protein subunit- and nucleic acid-based vaccines have emerged as highly promising areas of research. Two Chinese research teams have reported the efficacy of mRNA vaccines encoding IMV-specific proteins (M1R and A29L) and EEV-specific proteins (A35R and B6R), which exhibit high homology among OPVs. These vaccines have been shown to be effective at protecting BALB/c mice from lethal doses of MPXV and VACV, and they also demonstrate promising potential for cross-protection against other OPVs (Hou et al., 2023; Sang et al., 2023). Another study utilizing the highly conserved proteins A33, B5, and L1 from IMVs and EEVs, which were adjuvants with CpG-ODNs and alum, also demonstrated promising results, with vaccinated BALB/c mice showing significantly lower titers than the control group (Xiao et al., 2007). However, current studies on protein subunit- and nucleic acid-based vaccines have been limited primarily to animal models and *in vitro* studies.

The clear advantage of protein subunit- and nucleic acid-based vaccines lies in their ability to trigger fewer unwanted immune responses, thereby significantly reducing the potential for adverse effects compared to traditional calf lymph and cell culture vaccines, as they do not contain complete and active pathogens (Casey et al., 2005; Papukashvili et al., 2022).

## 7. Discussion

Following the elimination of the smallpox virus in 1982, the longstanding fear of poxviruses, which spanned centuries, began to fade from our collective memory. However, the recent pandemic of mpox highlights that these viruses, which have coevolved with their hosts for millions of years, have always posed a threat to human health. Mpox was initially regarded as a confined zoonotic disease, which limited comprehensive studies on its pathology in human hosts. Recent outbreaks underscore the vital lesson that geographically contained or eradicated diseases should not be underestimated. Viruses that are rapid and ever-evolving can unexpectedly transition from benign to highly pathogenic strains. Improved regulation of the animal trade is essential, as poxviruses swiftly adapt to new hosts and thus establish novel transmission patterns.

Moreover, individuals with HIV infection are notably vulnerable to MPXV, given the significant overlap between HIV and MPXV infections within the general population due to shared transmission routes. The prevalence of unawareness regarding MPXV among HIV-infected

individuals, as highlighted in recent studies, raises great public health concerns and emphasizes the need for vigilant surveillance and comprehensive health education efforts, particularly for those that partake in male-to-male intercourse (Gu et al., 2024).

The diverse hosts of MPXV, including rodents that act as potential reservoirs, cohabitate with humans in densely populated areas, thus complicating predictions of transmission. Concurrently, the discontinuation of smallpox vaccination in recent decades has left newer generations vulnerable to poxviruses. At present, there is no effective cure for mpox. Several studies have identified certain membrane proteins crucial for the transmission of MPXV, considering them as potential targets for antiviral drugs. However, the development of such drugs is still in its early stages (Lu et al., 2023), thus underscoring the urgency of comprehensively studying MPXV pathology.

MPXV shares numerous mechanisms against hosts with VACV, VARV, and other OPVs. However, MPXV also presents many unique traits. The immune evasion capacity of MPXV is particularly remarkable in human hosts, and many MPXV genes are truncated compared to their homologs, minimizing the immune response elicited by the infection while remaining fully functional. This characteristic makes vaccination less reliable for MPXV than for CPXV and some other poxviruses. Therefore, RNA- and epitope-based vaccines could be effective countermeasures against the stealth tactics employed by MPXV, resulting in an optimal immune response and protection.

The immune suppression capacity of MPXV also stands out, making it especially dangerous in immunodeficient individuals. As mentioned previously, HIV-infected patients tend to experience more severe symptoms and worse immunological outcomes following MPXV infection. All these factors make MPXV the most life-threatening poxvirus after the eradication of VARV, especially in the post-COVID-19 era.

Current research on MPXV faces multifaceted challenges. The adaptation of MPXV to various hosts and its intricate mechanisms for targeting specific tissues complicate controlled studies. Moreover, the distinctiveness of MPXV among OPVs presents additional hurdles, confounding attempts to study it reliably via prototypic or animal models. Additionally, the lack of clonal human antibodies that emulate the natural response of B cells to MPXV adds another layer of challenge to research the protective effects of antibody-mediated immunity against MPXV. However, amidst challenges lie opportunities. Notably, the ability of MPXV to promote immune evasion and suppression through its enduring coevolution with its hosts indicates that it is a remarkably successful species.

As our review demonstrates, two caspase-1 inhibitors, SPI-2 and CrmA, and the PKR antagonist protein K3 act as the phylogenomic hubs in MPXV that modulate the host immune environment. This makes understanding their related pathways pivotal. The ability of MPXV to suppress T-cell activation independent of MHC is still largely overlooked. This mechanism not only causes helper and cytotoxic T cells to be unable to react to MPXV-infected monocytes and granulocytes but also has a devastating impact on long-term immunological outcomes by disrupting germinal center formation. This unique mechanism employed by MPXVs remains overlooked in current studies.

MPXV and the human host share many homologous proteins, allowing MPXV to influence the host immune environment extensively. EEVs contain substantial amounts of host-originated proteins, protecting them from neutralizing antibodies and potentially reducing vaccine efficacy. These host-originated proteins could also potentially be extragenetic factors that allow some truncated MPXV genes to remain functional. Comprehensive metabolomic studies on MPXV infection should provide valuable insights in this regard but are currently lacking. Owing to the unique immune evasion ability of MPXV, research on other poxviruses offers limited reference value. Elucidating the regulatory patterns of metabolites and identifying their regulatory factors during MPXV infection is crucial for elucidating the unique immune modulation mechanisms of MPXV. These insights will significantly benefit the development of new vaccines or anti-MPXV drugs that can selectively regulate the

expression profile of factors involved in the immune evasion of MPXV, such as IL-18, free Ku heterodimers, CD28, caspase-1, and PKR, as discussed in this review. Alternatively, acute rejection caused by activation of the complement system poses a great challenge for patients undergoing xenotransplantation, and the evasion and suppression of the complement system by MPXV could inform the design of guided tools to intercept undesirable interactions between cytotoxic immune cells, tissues, or organs and foreign cells. Moreover, the capacity of MPXV to emulate the human immunological environment makes it a potential vessel for novel drug delivery systems. All of these examples illustrate how poxviruses can become indispensable tools in elucidating intricate aspects of immunity and in developing medicines.

## 8. Conclusions

In summary, investigations of MPXV have led to the adoption of a wide range of methods to overcome the immune response elicited by hosts. Understanding the immune response to MPXV and its evasion is crucial for developing treatments for mpox and other viruses, as well as advancing our understanding of the immune system.

## Conflict of interest

The authors declare no conflict of interest.

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