Cytokine 183 (2024) 156751

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Monkeypox (Mpox) vs. Innate immune responses: Insights into evasion mechanisms and potential therapeutic strategies

Pouya Pashazadeh Azari [a,1], Mohammad Rezaei Zadeh Rukerd [b,1], Javad Charostad [c], Davood Bashash [d], Niloofar Farsiu [b], Saleh Behzadi [e], Seyedeh Mahdieh Khoshnazar [b], Sajjad Heydari [a], Mohsen Nakhaie [b,f,*]

[a] Department of Immunology, Faculty of Medicine, Kerman University of Medical Science, Kerman, Iran
[b] Gastroenterology and Hepatology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
[c] Department of Microbiology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[d] Department of Hematology and Blood Banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[e] Student Research Committee, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[f] Clinical Research Development Unit, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran

ARTICLE INFO

Keywords:
Monkeypox
Orthopoxvirus
Innate immune response
Evasion
Treatment

ABSTRACT

Orthopoxviruses, a group of zoonotic viral infections, have emerged as a significant health emergency and global concern, particularly exemplified by the re-emergence of monkeypox (Mpox). Effectively addressing these viral infections necessitates a comprehensive understanding of the intricate interplay between the viruses and the host's immune response. In this review, we aim to elucidate the multifaceted aspects of innate immunity in the context of orthopoxviruses, with a specific focus on monkeypox virus (MPXV). We provide an in-depth analysis of the roles of key innate immune cells, including natural killer (NK) cells, dendritic cells (DCs), and granulocytes, in the host defense against MPXV. Furthermore, we explore the interferon (IFN) response, highlighting the involvement of toll-like receptors (TLRs) and cytosolic DNA/RNA sensors in detecting and responding to the viral presence. This review also examines the complement system's contribution to the immune response and provides a detailed analysis of the immune evasion strategies employed by MPXV to evade host defenses. Additionally, we discuss current prevention and treatment strategies for Mpox, including pre-exposure (PrEP) and post-exposure (PoEP) prophylaxis, supportive treatments, antivirals, and vaccinia immune globulin (VIG).

1. Introduction

Monkeypox (Mpox) is an infectious disease caused by the monkeypox virus (MPXV), a rare zoonotic pathogen first discovered in laboratory primates in Denmark in 1958, and the first human case was identified in 1970 in an unvaccinated 9-month-old from the Democratic Republic of the Congo during the smallpox eradication program [1–4]. MPXV is characterized by its large envelope and double-stranded DNA structure and belongs to the poxviridae family and the orthopoxvirus genus, which includes other members such as variola virus (VARV), cowpox virus (CPXV), vaccinia virus (VACV), camelpox virus (CMLV), taterapox virus (TATV), and ectromelia virus (ECTV) [1,4–8].

Smallpox, a lethal disease caused by the variola virus (VARV) with a mortality rate of approximately 30 %, may have caused more human deaths over the past two millennia than any other single disease due to its high fatality rate and endemic presence. Following extensive vaccination campaigns in the 19th and 20th centuries, the World Health Organization (WHO) declared smallpox eradicated in 1979 [9]. Vaccination against smallpox offers significant protection against orthopoxvirus infections, including Mpox, resulting in an 85 % decrease in the incidence of Mpox among individuals who have received the smallpox vaccine [10–12]. Consequently, individuals born after 1980 who have not been vaccinated against the smallpox virus are susceptible to Mpox between the years 2000 and 2020 [10]. Between 1970 and 1986, a total of 10 cases of Mpox were recorded in West African countries, including Sierra Leone, Nigeria, Liberia, and Côte d'Ivoire. In contrast, a

* Corresponding author at: Gastroenterology and Hepatology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran.
E-mail address: mohsennakhaee1367@gmail.com (M. Nakhaie).
[1] Pouya Pashazadeh Azari and Mohammad Rezaei Zadeh Rukerd contributed equally to this work.

https://doi.org/10.1016/j.cyto.2024.156751
Received 16 June 2024; Received in revised form 16 August 2024; Accepted 4 September 2024
Available online 7 September 2024

significantly higher number of cases, specifically 394, were reported in the Democratic Republic of the Congo, Cameroon, and the Central African Republic during the same period [13]. The sample obtained from the Congo Basin, which is referred to as the Central Africa clade, exhibits greater disease severity, pathogenicity, and human-to-human transmission rates compared to the sample isolated from West African nations, known as the West Africa clade [14]. Furthermore, the Central Africa clade displays a mortality rate of 10.6 %, whereas the West Africa clade exhibits a mortality rate of 3.6 %. This disparity in death rates further underscores the heightened danger associated with the Central Africa clade [10]. The re-emergence of Mpox in Bayelsa State, Nigeria, after 39 years, along with the transmission of the virus by travelers from Nigeria to different regions of the world in 2018 and 2019, has sparked concerns regarding the potential resurgence of the virus in previously depleted ecological and immunological niches left behind by the eradication of the VARV [15]. The rapid increase in the number of Mpox cases during the COVID-19 pandemic has triggered global concern and piqued international interest in this disease [16]. On May 6, 2022, a Mpox outbreak was detected, originating from a British individual who acquired the infection while visiting Nigeria, an endemic region [17,18]. Finally, the WHO declared mpox a Public Health Emergency of International Concern (PHEIC) in July 2022 [19–21], and according to WHO data, from January 1, 2022, to April 30, 2024, 117 countries reported a cumulative total of 97,208 laboratory-confirmed Mpox cases, including 186 deaths [22]. Recent outbreaks, as reported by the Centers for Disease Control and Prevention (CDC), show a higher prevalence of Mpox cases among individuals aged 26 to 40 [23].

Innate immunity acts as the first line of defense, playing a crucial role in protecting the body against multiple pathogens, including poxviruses [24–26]. In the early stages of infection, components of the innate immune system like Innate immune cells, such as natural killer (NK) cells, dendritic cells (DC), and granulocytes, interferons (IFN), and the complement system are responsible for controlling infection until adaptive immune responses are activated. Inflammatory cells play a significant role in the primary defense against poxviruses by engaging in phagocytosis and producing reactive oxygen species (ROS). IFNs play a crucial role in the initial defense against poxviruses by inducing an antiviral state in cells and activating various immune cells, including macrophages, NK cells, and cytotoxic T cells (CTL). The complement system out of the three pathways available for activation, only two classical and alternative pathways are active against poxvirus, resulting in the development of the membrane attack complex (MAC) [24]. In the direction of confrontation, orthopoxviruses including MPXV have been observed to frequently employ immune evasion strategies, which play a significant role in their pathogenesis. [27,28].

In this review, we aim to elucidate the multifaceted aspects of innate immunity in the context of orthopoxviruses, with a specific focus on MPXV. We analyze the roles of key innate immune cells—NK cells, DCs, and granulocytes—in defending against MPXV, along with the IFN response involving toll-like receptors (TLRs) and cytosolic DNA/RNA sensors. We examine the complement system's role and MPXV's immune evasion strategies. Additionally, we discuss current Mpox prevention and treatment strategies, aiming to enhance understanding and propose solutions for managing and mitigating Mpox outbreaks.

2. Innate immune cells

2.1. Natural killer (NK) cells

NK cells are a key component of innate immunity and play a crucial role in connecting innate and adaptive immune responses against viral infections. They contribute to the innate immune response and facilitate communication between the two immune systems [29–31]. NK cells can be activated or inhibited through the interaction of receptors on their surface with ligands present on target cells. One example of such ligands is the major histocompatibility complex I (MHC-I) molecules displayed on the surface of target cells [29,32,33].

Upon activation, NK cells perform their functions in combating viral infections by: 1) Inducing direct killing of virus-infected cells through cell-to-cell interactions and the secretion of granules that contain perforin and granzymes, and 2) Releasing modulatory cytokines like IFN-γ and tumor necrosis factor-alpha (TNF-α) to regulate inflammatory responses and interact with dendritic cells, promoting T-helper 1 cell polarization [29,34–39].

Research conducted on ECTV has identified CD94 as a crucial molecule contributing to the resistance of C57BL/6 mice against this disease [40]. CD94 is a molecule present in NK cells that has the ability to form a heterodimer with NKG2A, NKG2C, and NKG2E (Fig. 1). CD94-NKG2A functions as a suppressor receptor, whereas CD94-NKG2C and CD94-NKG2E act as activating receptors. In the case of ECTV infection, it has been discovered that CD94-NKG2E specifically binds to the MHC class Ib molecule (Qa-1b in mice and HLA-E in humans) expressed on the surface of ECTV-infected cells. This interaction, along with the synergistic effect of the activating receptor NKG2D, triggers the activation of NK cells. Upon activation, the activated NK cells migrate to lymph nodes and employ the aforementioned mechanism to eliminate virus-infected cells, leading to the destruction of the infected cells [40]. Since the function of CD94-NKG2 heterodimers is conserved between rodents and primates, and similarity in viral sequences suggest that the mechanisms of NK cell response against viruses like MPXV and VARV are likely to be similar in humans and mice. However, there may be species-specific variations in the details of these interactions and immune responses, and further research is needed to fully understand these nuances [40].

NK cells are indispensable in the defense against MPXV [41]. MPXV results in the robust expansion of all subsets of NK cells in both the bloodstream and lymph nodes [29]. Within a week of MPXV infection, the effectiveness of NK cells is compromised as the virus diminishes the expression of chemokine receptors crucial for NK cell migration, cytotoxicity, and the secretion of IFN-γ and TNF-α [29]. According to a study conducted on rhesus macaques, MPXV stimulates the proliferation of NK cells in both the blood and lymph nodes and serve as a significant source of type I and type II IFNs. While the production of IFNs by NK cells can restrict the proliferation of VACV and enhance the survival of infected mice, NK cells alone are unable to completely eliminate the virus without the assistance of CD8 + cells [42]. In the initial week of Mpox, the virus employs a countermeasure by diminishing the function of NK cells. This is accomplished by reducing the expression of chemokine receptors that are critical for NK cell migration, cytotoxicity, and the secretion of IFN-γ and TNF-α cytokines [41]. Following Mpox in nonhuman primates (NHP), there is an observed increase in the proliferation and number of NK cells in both the blood and lymph. However, it has been found that the expression of CD107a, a marker used to assess cytotoxic capacity and cytokine secretion (such as IFN-γ and TNF-α), is reduced in most subtypes of NK cells. This indicates a decrease in the functional capability of NK cells after MPXV infection [29].

The alteration in NK cell function, characterized by reduced cytotoxicity and cytokine secretion, can lead to a diminished ability to directly eliminate infected cells and dampen the adaptive immune response. However, there is a subsequent recovery observed in chemokine receptor expression and an increase in CD107a levels on days 7 and 8 post-infection. This restoration of NK cell activity partially contributes to virus clearance during the later stages of infection [29].

The significance of NK cells was further elucidated through studies conducted on Castaneous mice, which are naturally susceptible to orthopoxviruses. These mice exhibit low levels of the cytokine IFN, which is likely attributed to the absence of NK cells. In one particular study, the injection of IL-15, a cytokine that stimulates NK cell production, resulted in a temporary increase in the number of NK cells. Remarkably, these mice exhibited enhanced resistance to infection with MPXV and VACV, indicating the crucial role of NK cells in conferring protection against these viruses [43,44].

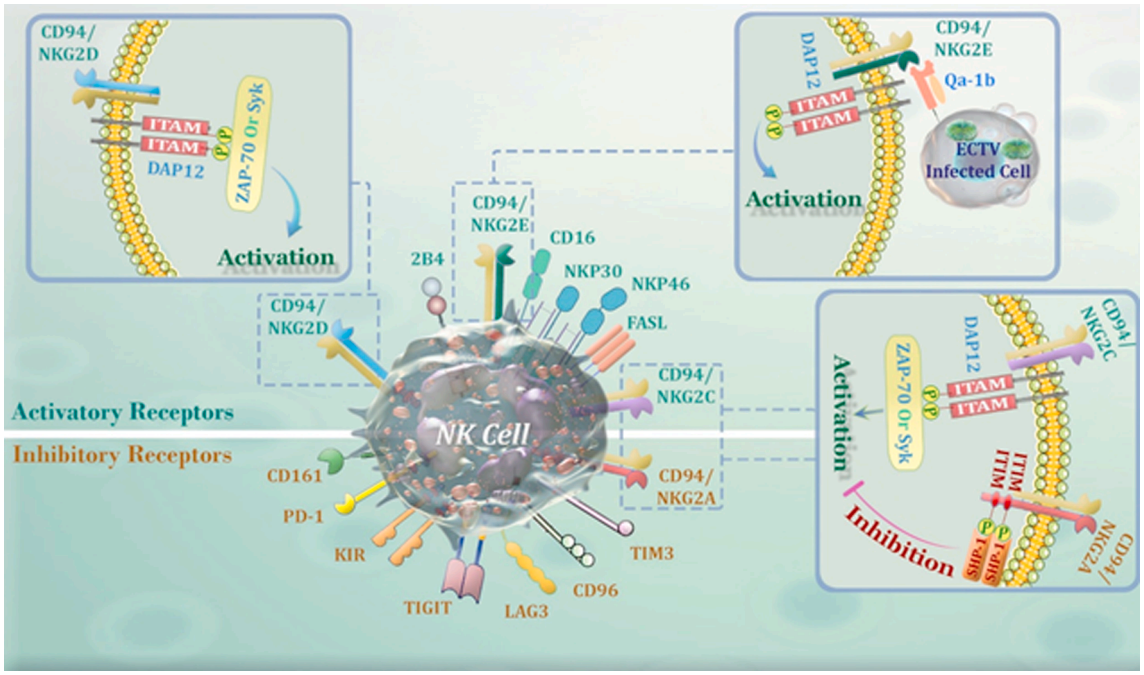

Fig. 1. The contribution of CD94 in natural killer (NK) cell activation or inhibition during poxvirus infection.

2.2. Dendritic cell (DC)

DCs play a vital role in innate immune responses through the production of antiviral cytokines, including IFN-α. Additionally, they serve as key activators of the immune system by presenting antigens to acquired immune cells, facilitating the initiation of adaptive immune responses [45]. The production of IFNs in plasmacytoid dendritic cells (pDCs) occurs through a pathway dependent on TLRs s and the adapter protein myeloid differentiation primary response 88 (MyD88). Unlike other innate immune cells, pDCs primarily utilize this TLR-MyD88-dependent pathway and do not heavily rely on other pattern recognition receptors (PRRs) for IFN production [31]. The role of DCs has been well established through studies conducted on poxviruses like VACV and ECTV. In a mouse study, it was observed that VACV infection triggered the production of cytokines such as IL-1, IL-6, IL-12, and IFN-β by classical dendritic cells (cDCs) (Fig. 2A). On the other hand, ECTV infection stimulated the production of IFN-α and IL-6 specifically in pDCs, which are crucial for recovery from primary infection (Fig. 2B). These findings highlight the distinct cytokine profiles and roles of different dendritic cell subsets in response to poxvirus infections [31,46].

Poxviruses exhibit a cytopathic effect characterized by different outcomes in various cell types. In non-antigen presenting cells, poxviruses induce cell lysis, resulting in the destruction of the infected cells. However, in antigen presenting cells (APCs) such as macrophages, DCs, and B cells, the cytopathic effect of poxviruses leads to apoptosis, a programmed cell death process. Further studies have revealed that during vaccinia virus infection, DCs do not fully mature. This incomplete maturation prevents the proper surface expression of stimulating molecules when presenting antigens. Consequently, this impaired presentation leads to a state of anergy or tolerance, where the immune response is suppressed. The observed apoptosis in these infected DCs is not an escape mechanism employed by the virus to eliminate APCs. Rather, it appears to be a protective mechanism aimed at preventing anergy or tolerance induction and promoting a functional immune response (Fig. 2C) [47–49].

DCs are essential for survival against ECTV. Studies have shown that the survival of ECTV-infected mice relies on the presence of specific subsets of DCs. When pDCs or CD8 + DCs were individually removed from the lymph nodes of infected mice, the mice did not succumb to the infection. However, when both pDCs and CD8 + DCs were simultaneously depleted, the infected mice were unable to mount an effective defense and eventually died. This indicates that while each subset of DCs has some level of antiviral activity on its own, the combined presence of both subsets is essential for optimal resistance against ECTV [50].

2.3. Granulocytes

Granulocytes, including neutrophils, eosinophils, and basophils, play a vital role in the control of viral infections. These cells contribute to the immune response against viruses by performing several functions. Firstly, they can phagocytize virus-infected cells, effectively eliminating the source of viral replication. Additionally, granulocytes secrete cytokines and chemokines that help to coordinate and activate other immune cells, such as dendritic cells, T cells, and natural killer cells, to mount an effective antiviral response. This interplay between granulocytes and other immune cells helps to limit viral spread and promote the clearance of viral pathogens from the body [46,51].

The presence of granulocytes is crucial for the resistance of mice against ECTV infection. Studies have shown that when granulocytes are depleted from ECTV-resistant mice, their susceptibility to the virus increases. This highlights the important role of granulocytes in the immune response against ECTV. Furthermore, granulocytes have been found to influence B cell responses, including the production of protective antibodies, against this virus [46].

In a study involving NHP leukocytes infected with CPXV and MPXV, researchers observed a significant presence of stained cells expressing pox antigens, particularly in monocytes and granulocytes, specifically neutrophils. The results of this study indicated that NHPs exhibited more severe symptoms in CPXV and MPXV infections when positively stained monocytes and granulocytes were identified [29].

Based on the reviewed studies, NK cells, DCs, and granulocytes have been found to play crucial roles in combating viral infections, including poxviruses. These immune cells contribute to the defense against poxviruses by producing chemokines and cytokines, such as type I IFNs, which are involved in antiviral immune responses. In contrast, other immune cells may be less effective in providing defense against poxviruses. Notably, CTL cells and the functions mentioned are important

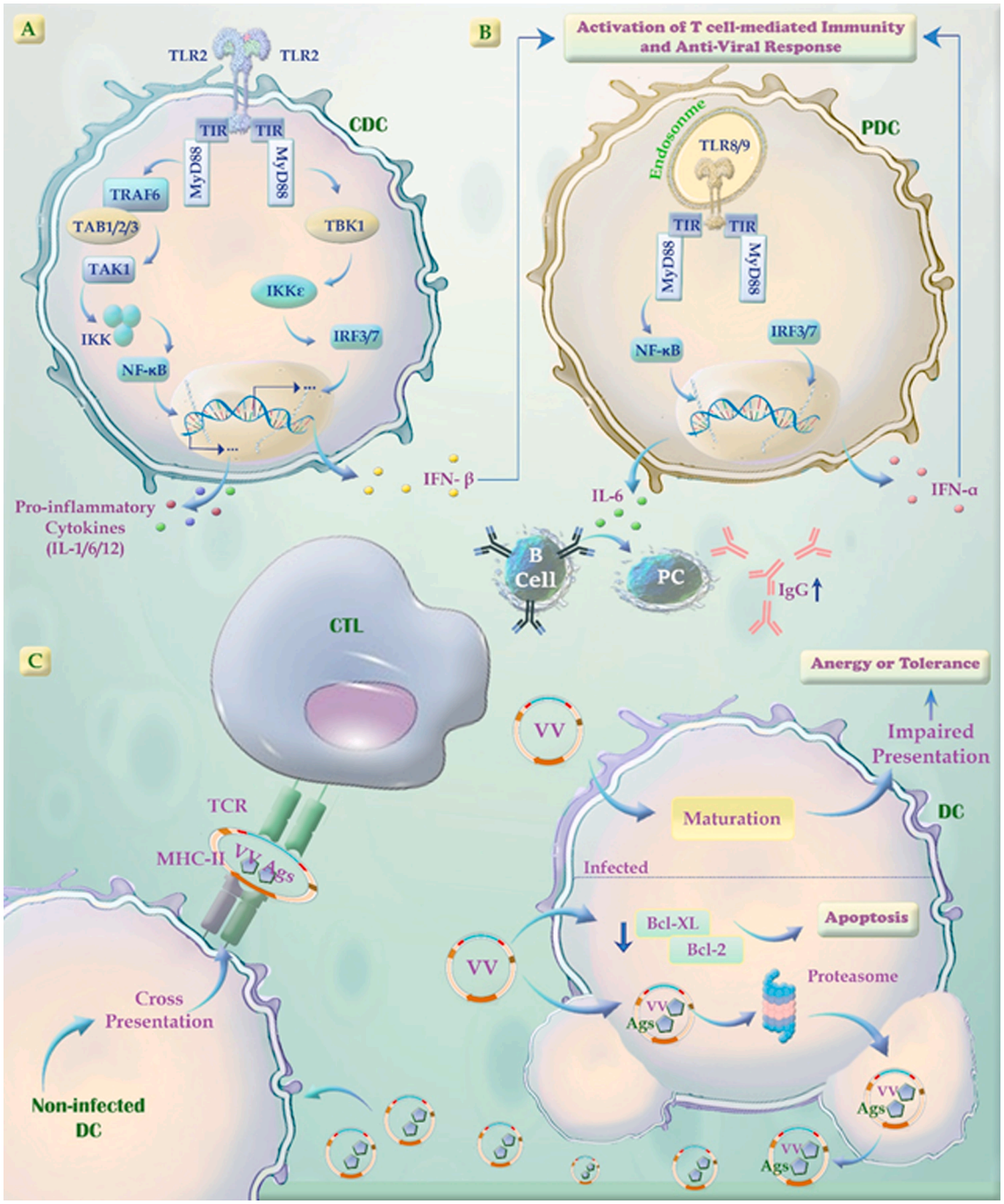

Fig. 2. The role of dendritic cell (DC) against poxviruses infection. A) plasmacytoid dendritic cells (pDC) activation and cytokines production during vaccinia virus (VACV) infection. B) pDC activation and cytokines production during ectromelia virus (ECTV) infection. C) The cytopathic effect of poxviruses in DC.

components of the innate immune response against poxviruses. Given the similarities between different poxviruses, it is reasonable to speculate that these immune cells may also play similar roles in Mpox infection.

3. Interferon (IFN)

The type I IFNs, including IFN-α and IFN-β, play a crucial role in the first line of host defenses by inducing an antiviral state in host cells, activating a wide range of antiviral effectors to eliminate invading multiple pathogens, and effectively inhibiting poxvirus replication during the early stages of viral entry [52–54]. These cytokines activate various cellular antiviral pathways, leading to the production of antiviral proteins that restrict viral replication and spread [52].

Type-I IFNs play several roles in establishing an antiviral state. Firstly, they inhibit viral replication within infected cells by interfering with various stages of the viral life cycle, including blocking viral entry, inhibiting viral gene expression, and impeding viral protein synthesis and assembly. By doing so, the production of new virus particles is limited, helping to contain the infection. Secondly, these IFNs are crucial in the activation and antigen presentation process. They promote the maturation and activation of antigen-presenting cells, such as DCs, which are essential for initiating adaptive immune responses. Enhanced antigen presentation facilitates the recognition of viral antigens by immune cells, particularly B and T cells, leading to the generation of specific immune responses against the virus. Lastly, type-I IFNs act as a

bridge between innate and adaptive immunity, activating innate immune cells such as NK cells and macrophages, and contributing to the initiation of acquired immune responses [55]. Additionally, IFN-β, when administered 6–8 h post-infection, significantly suppressed MPXV in vitro, demonstrating its potential as a therapeutic agent by inducing the antiviral protein MxA, whose continuous expression was shown to block MPXV infection [56].

3.1. Toll-like receptors (TLRs) – TLR 3,7/8,9

Recognition of viral DNA and RNA by TLRs triggers several pathways that lead to the production and secretion of IFN-I. Here are the pathways involved: 1) TLR3 and the TIR-domain-containing adapter-inducing interferon-β (TRIF) pathway: TLR3 recognizes viral double-stranded RNA (dsRNA). Upon recognition, TLR3 activates downstream signaling through TRIF, resulting in the production and secretion of IFN-I, 2) TLR7/8 pathway: TLR7 and TLR8 recognize viral single-stranded RNA (ssRNA). Activation of TLR7/8 leads to the activation of signaling pathways that induce the production and secretion of type I IFN, and 3) TLR9 and MyD88 pathway: TLR9 recognizes viral double-stranded DNA (dsDNA) and unmethylated CpG motifs. TLR9 activation triggers downstream signaling through the adapter protein MyD88, leading to the production and secretion of type I IFN (Fig. 3) [57–60].

Poxviruses, with their long dsDNA genomes, are generally expected to be primarily recognized by TLR9, which detects viral dsDNA. Additionally, cytosolic DNA receptors also play a role in sensing poxvirus infection. However, the immune response to poxviruses is a complex interplay of various factors. For instance, studies have shown that mice lacking TLR9 exhibit increased susceptibility to ECTV, an orthopoxvirus that causes mousepox. This suggests that TLR9-mediated recognition of poxvirus DNA contributes to host defense against these viruses. Moreover, TLR9 signaling is involved in the production of IFN-α, an important antiviral cytokine [1,45]. In another study, TLR4(−/-), TLR2(−/-), TLR7(−/-) mice were resistant to ECTV infection, but TLR9(−/-) and MyD88(−) mice were susceptible [61]. A study on mouse pDCs, on the other hand, found that recognition of vaccinia virus or its DNA is dependent on TLR8 and MyD88 rather than TLR9. According to the results of this study, the mouse TLR8 ligand infected with vaccinia virus has an A/T-rich genome and viral AT-rich islands [62]. While TLR9 and TLR8 have been shown to have a positive effect in identifying the virus and inducing an IFN response, TLR3 identification and signaling is linked to an increase in vaccinia virus multiplication as well as pathogenicity. The researchers discovered that knocking out the TLR3 gene significantly reduced the virus's spread, proliferation, and lethality in TLR3(−/-) mice [63].

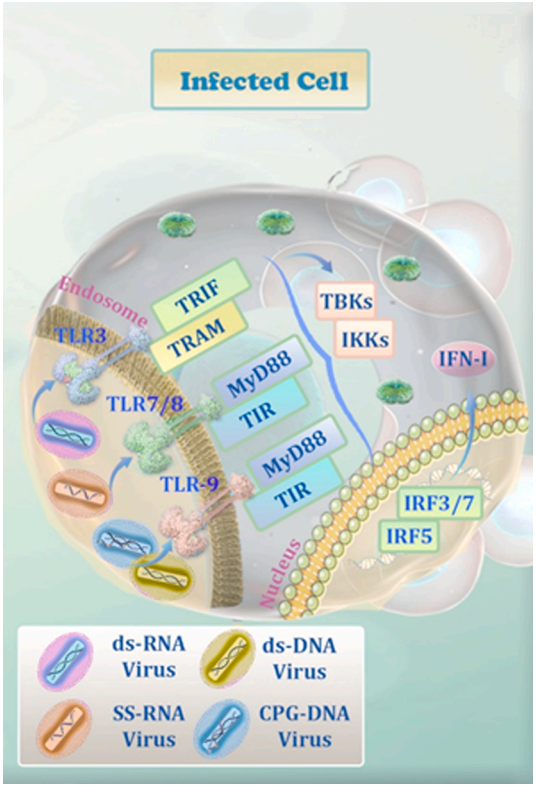

Fig. 3. The function of toll-like receptors (TLRs) in type-I IFNs production during viral infections.

In summary, TLR9, TLR8, and the adapter protein MyD88 have been identified as key components involved in the recognition of orthopoxviruses and the stimulation of the IFN-α response. TLR9 plays a crucial role in recognizing viral dsDNA, while TLR8 recognizes viral ssRNA. The engagement of these TLRs activates downstream signaling pathways involving MyD88, leading to the production of IFN-α and establishment of an antiviral state.

3.2. Cytosolic DNA/RNA sensors

An interesting finding is that the recognition of Modified Vaccinia virus Ankara (MVA), which is a modified version of wild VACV, by melanoma differentiation-associated protein 5 (MDA-5) leads to an increased production of IFN-β in THP-1 cells, which are human monocyte cells [63]. In the study conducted by Boone and colleagues, it was observed that a significant proportion (15 %) of the viral mRNAs encoded by the DNA virus form hybrid structures with each other in the cytosol. These hybrid structures result in the production of dsRNA molecules. Importantly, these dsRNA hybrids exhibit resistance to degradation by cellular ribonucleases (RNases). The presence of these dsRNA hybrids in the cytosol triggers the activation of cytosolic dsRNA receptors, such as MDA-5. Upon recognition of the dsRNA hybrids, MDA-5 initiates a signaling cascade that leads to the production of IFN and other antiviral cytokines [64].

MDA-5 interacts with a protein in the mitochondrial membrane called mitochondrial antiviral signaling protein (MAVS) after recognizing the RNA hybrids. This interaction will activate the IRF3 transcription factor, resulting in the transcription of type I IFN. MAVS also causes apoptosis in virus-infected cells, which is another mechanism for creating an antiviral state [63].

Cyclic GMP–AMP synthase (cGAS) is an enzyme that binds to DNA in the cytosol, with this DNA being triggered by the presence of invading agents inside the cell, playing a crucial role in antiviral defense. The product of cGAS is cyclic GMP-AMP (cGAMP), which binds and activates the transcription factors NF-κB and IRF3, resulting in the production of type I IFN by binding to stimulator of interferon genes (STING) [65,66].

Furthermore, cGAMP can be released from infected cells and activate the transcription factors mentioned above in cells that have not yet been infected with the invading agents. The removal of cGAS or STING from mouse and human cells was associated with decreased type I IFN production in cells infected with MVA, indicating the importance of the cGAS-cGAMP-STING axis in identifying and fighting poxviruses [67].

4. Complement system

The Complement system is one of the major mechanisms of inflammation as a main component of the innate immune response in a primary host immune system [68,69]. The complement system is activated by three different pathways: the classical, the alternative, and the mannan-binding lectin pathway. These pathways lead to the assemblage of different C3 convertases. The C3 convertases are serine proteases that cleave C3 into two fragments, C3a and C3b. After the C3 cleavage, the three initiating pathways converge on a common pathway that led to the formation of the C5 convertase [70]. C5 convertase enzymes convert C5 into C5b, which together with C6, C7, C8 and numerous copies of C9

forms a MAC pores [71]. The complement cascade activation contributes to the resolution of viral infection due to multiple mechanisms [72].

The genomes of some orthopoxviruses, such as Smallpox, CPOX, VACV, and MPXV, encode poxviral inhibitors of complement enzymes (PICEs) that can control complement activation, which include four short consensus repeat (SCRs) and are similar to human complement control protein (CCP) [70,72].

VACV contains the gene which directs the production of vaccinia virus complement-binding protein (VCP), that this protein is an important virulence factor in the pathogenesis of this virus by protecting both infected cells and virions [72–74]. Other orthopoxviruses express VCP homologs that are essential for virulence. The VCP homolog in the smallpox virus is called the smallpox inhibitor of complement enzymes (SPICE) [70,75]. In SPV, SPICE is remarkably more potent in complement system inhibition than VACV [76]. The CPOX carries the VCP homolog gene that makes an inflammation modulatory protein (IMP), which provides instructions for proteins that inhibits the inflammatory reaction that develops in response to the viral infection [77].

VCP, the 35-kDa protein, is a complement system inhibitor obtained from virally infected cells and has similarities to complement regulatory proteins (CRPs), including membrane cofactor protein (MCP;CD46), C4b-binding protein alpha chain, Factor H, and decay-accelerating factor (DAF;CD55), complement receptors type 1 (CR1) and 2 (CR2), and the regulatory-sites for C3b and C4b [68,70,78]. Among the roles of VCP, the following can be mentioned: 1. binding to the C3b and C4b constituents of the complement system which inhibit the release of the anaphylactic and chemotactic mediators such as C3a and C5a and interact with the formation of the membrane attack complex (MAC); 2. inhibit virus neutralization via the complement system, which is triggered by the antibodies; 3. blocking the complement cascade by interferes with classic and alternative complement pathways; 4. binding to the heparin-like molecules of endothelial cells, therefore inhibit the chemotaxis signal transduction [69,79–83].

Based on genomic analysis, several MPXV strains of central and west African origin have been assumed to probably be responsible for the increased virulence of central African strains of MPXV, one of which is the D14L gene that encodes the monkeypox inhibitor of complement enzymes (MOPICE), the 24 kDa secretory protein and ortholog of VCP, acts as a complement inhibitor [72,84,85]. The Central African MPXV strains demonstrated to encode a truncated structure of this protein because of an early reading frame termination in the MOPICE. However, the related gene (D14L) is completely deleted in the Western African strains, which may further reduce the virus pathogenicity and mortality for humans compared with Central African MPXV [69,77].

Despite of protein truncation in Central African MPXV, studies suggested that MOPICE from a Congo basin isolate had some complement enzyme inhibitory activity and more fully establish the role of MOPICE as a potential virulence factor for the Central African MPXV and its inhibitory activity for human complement proteins was described [14,79].

MOPICE simulates the action of CCP, serves as a cofactor for the serine protease factor I, which can cause C3b and C4b inactivation, and also bound with C3b and C4b, and indicated cofactor activity for these proteins which can cause C3 and C5 convertase inhibition in complement cascades [14,86,87].

The absence of a MOPICE could cause Mpox and infected cells to be more sensitive to antibody and complement lysis, which could reduce virus spread and severity [14].

5. Monkeypox immune evasion

Immune evasion is a mechanism used by pathogens to escape host defense mechanisms. The majority of the information available on orthopoxvirus immune system evasion has come from studies on VACV [88].

Protein kinase R (PKR), which is well targeted by poxviruses, is one of the proteins that plays an important role in the host's immune system. PKR is monomeric and inactive in host cells; this protein dimerizes in the presence of dsRNA, which is produced during viral replication of many viruses, and is then autophosphorylated to become active.

The active form of PKR has several functions in the host's immune system, including: 1) Phosphorylating the α subunit of the eukaryotic translation initiator factor 2 (eIF2), disrupts viral mRNA translation and the transfer of methionyl tRNA to the ribosome, preventing the virus from multiplying in the host cell, 2) Contribution in signal transmission by phosphorylating the immune response factor 3 (IRF3), which initiates the transcription of IFN genes, 3) Phosphorylating IκBα and activate NF-κB; To activate the transcription factor NF-κB, its inhibitory factor, IκBα, must be phosphorylated; This phosphorylation allowing genes such as TNF-α, IL-1b, and IL-6 to be transcribed and expressed, and 4) Upregulating IFN induction by MDA-5 causes increases IFN production in the dsRNA recognition pathway [89–92] (Fig. 4A).

The vaccinia E3L gene is important in preventing the formation of IFN responses in host cells [88]. The E3L gene naturally encodes two proteins in the virus, which are known as P25 and P20. The P25 protein contains 190 amino acids and is the full form of the E3L product, whereas the p20 protein, which is the shortened form of p25, is the result of the start of translation from methionine codon 38, making p20, 37 amino acids shorter than the N-terminal end of P25 [93]. Vaccinia E3 gene products contain two C-terminal and N-terminal domains. Both domains were found to be required for full virulence of wild-type vaccinia in mice [88,94].

The C-terminal domain, which is identical in p25 and p20, contains a double-stranded RNA-binding domain (dsRBD). C-terminal binding to viral dsRNA keeps the dsRNA hidden and out of reach of the host immune system, interfering with the function of many viral dsRNA sensors found in host cells [95,96].

The N-terminal domain's functions include direct inhibition of PKR activity and binding to Z-DNA [97,98]. Concerning the role of PKR inhibition, it should be noted that in the late stages of vaccinia virus infection, we see an excessive accumulation of dsRNAs that are more volatile than the capacity of the C-terminal domains of E3, and as a result, the virus will not be able to hide all of this dsRNA [97].

VACV E3LΔ37N is a vaccinia variant that does not encode 37 amino acids from the N-terminus and instead encodes a p20-like protein. This variant's lethality dosage (LD50) has been determined to be 50 times lower than the wild type of vaccinia. These findings indicate that the second N-terminal plays an important role in vaccinia's full virulence; in other words, the presence of the second N-terminal is required for vaccinia to effectively escape immune system mechanisms [96,98].

The F3L gene of the MPXV encodes a protein that is homologous to the products of the vaccinia E3L gene. The genomic comparison of MPXV and VACV reveals striking similarities in their genes [88] (Fig. 4B). The F3 protein of MPXV functions as an evasion strategy by binding dsRNA and thereby reducing IFN production [99].

It was previously demonstrated that shortening the N-terminal end of vaccinia weakened virulence [96–98]; however, contrary to expectations, MPXV is able to completely deactivate the PKR pathway and effectively replicate and cause disease in the host cell; in other words, MPXV has an IFN-resistant phenotype and a host spectrum similar to wild-type vaccinia and is able to inhibit host cell antiviral immunity more effectively than the VACV E3LΔ37N (which has the same N-terminal truncation as MPXV) [88].

In addition to inhibiting PKR function by the MPXV F3 protein, this virus is able to cover its short N-terminal by reducing the accumulation of dsRNAs caused by replication, because, as previously stated, the second N-terminal was required to inhibit PKR function in the case of excessive accumulation of dsRNAs [97,100].

Other proteins in MPXV that contribute to the disruption of the host's immune system include (Fig. 4C): BR-203 gene products that prevent lymphocyte apoptosis in virus-infected lymphocytes play a role in virus spread in the host's body. The A44L gene product encodes the 3-b-

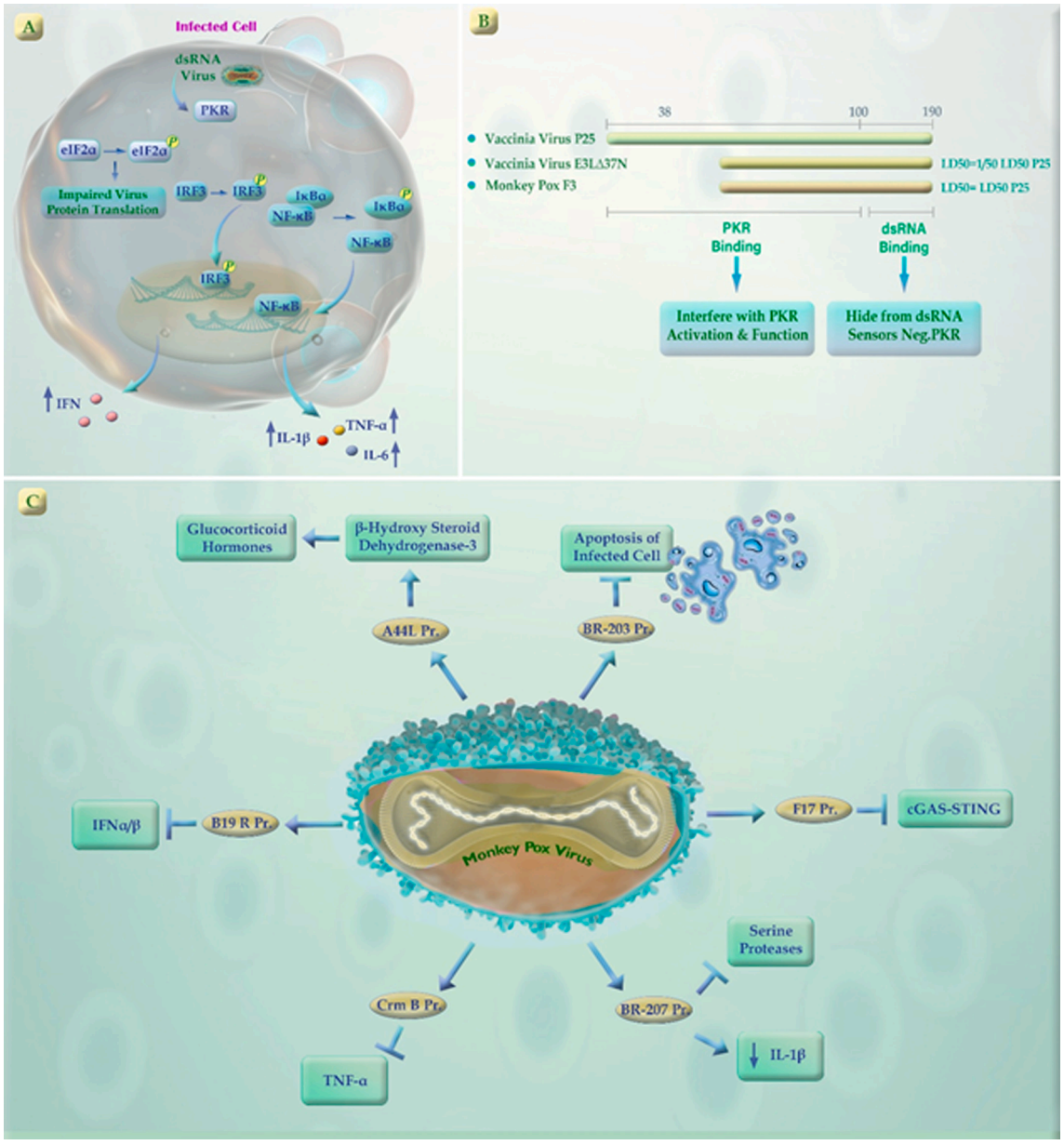

Fig. 4. Immune evasion of monkeypox virus (MPXV). A) The function of activated protein kinase R (PKR) in the immune system of the host. B) The ability of the MPXV F3L, vaccinia virus P25, and vaccinia virus E3L37N to suppress immunological responses. C) MPXV proteins that contribute to the host's immune system being thrown off balance.

hydroxysteroid dehydrogenase enzyme; this enzyme increases the production of glucocorticoid hormones in the host, which are known immune suppressors. The B19R protein binds to IFN-α and IFN-β, preventing them from binding to their receptors and functioning. BR-05/BR-226, also known as cytokine response modifiers B (crmB), bind to TNF-α and prevent it from binding to the corresponding receptor and functioning. BR-05/BR-226—207, which are known as serine protease inhibitors (SPI-1). To produce and secrete IL-1, the caspase 1 enzyme must first cut the inactive and pre-made form of Pro-IL-1 and convert it to the active form of IL-1. Caspase 1, a member of the serine protease family, is inhibited by BR-207, causing the production of active IL-1 to be disrupted. F17 is a protein that disrupts the regulation and balance of mTORC1 and mTORC2, ultimately preventing the function of the cGAS-STING axis. This axis, as previously stated, is important in identifying the DNA of viruses, including poxviruses [84,92,101].

6. Monkeypox prevention and treatment strategies

Managing monkeypox effectively requires enhanced infection control measures, good hygiene practices, and vaccinia virus vaccination. Preventive strategies include avoiding contact with infected animals and humans, using personal protective equipment, isolating the sick, practicing proper hand hygiene, and employing smallpox vaccines to control transmission during outbreaks. The increase in Mpox cases is partly due to more frequent animal-human interactions and heightened international travel. Preventing disease spread requires avoiding contact with sick animals, materials, and people. Contributing factors to the resurgence of Mpox include a lack of specialized vaccines and a growing global population [102–104].

Treatment is recommended for those with severe Mpox, high-risk individuals (immunocompromised, children, those with dermatitis, pregnant or breastfeeding women, or those with complications), and cases involving infection in critical areas (mouth, eyes, genitals, or

anus). For most, care is symptomatic and supportive. Although there is no specific treatment for Mpox, smallpox antiviral drugs may be effective due to genetic similarities [105]. Despite some progress, accelerating drug research against Mpox is vital to prevent long-term outbreaks and drug-resistant strains. Key priorities include enhancing drug specificity and delivery for precise targeting and efficient transmission, developing drugs less likely to provoke resistance, and exploring sequential and combination therapies to tackle different infection stages and variants. Additionally, reducing drug toxicity is essential to minimize adverse effects. Early and intensified drug development efforts are crucial to effectively address the ongoing global Mpox outbreak and prepare for future public health challenges [106].

6.1. Prevention

6.1.1. Pre-exposure (PrEP) prophylaxis

The data indicates that receiving the smallpox vaccine in the past may offer protection against MPXV and improve symptoms [107–109]. Pre-exposure prophylaxis (PrEP) is the most effective strategy for controlling a MPXV outbreak, especially for high-risk groups such as men who have sex with men (MSM) and front-line health workers, including those in research and clinical laboratories performing orthopoxvirus diagnostics and designated response teams [109–111]. In the United States Strategic National Stockpile, there are three smallpox vaccines available: JYNNEOS® (also known as IMVAMUNE, IMVANEX, MVA-BN), ACAM2000®, and the Aventis Pasteur Smallpox Vaccine (APSV) which can be used for smallpox under an investigational new drug (IND) protocol. The differences between JYNNEOS® and ACAM2000® are summarized in Table 1. Table 2 summarizes the contraindications for using ACAM2000® and JYNNEOS® for PrEP according to ACIP guidelines [110].

6.1.2. Post-exposure (PoEP) prophylaxis

MPXV is transmitted through prolonged and close contact with an individual showing symptom of the disease. Short interactions and those with the use of proper protective gear are not considered high-risk and do not require post-exposure prophylaxis (PoEP) [112]. The Centers for Disease Control and Prevention (CDC) provides guidance on assessing exposure risks and making informed decisions about PoEP. If vaccination is administered within four days of exposure, disease onset can be prevented. If given between four and fourteen days after exposure, vaccination may reduce symptoms but may not prevent the disease [112].

High-risk exposure includes unprotected contact with bodily fluids, skin, mucous membranes, or contaminated materials, as well as being within six feet of a patient during procedures that may produce aerosols

Table 1
Prevention and treatment strategies against Mpox virus infection.

Vaccines					
Name	Type	Indication	Major Side Effects	Administration	Ref.
JYNNEOS® (also known as Imvamune or Imvanex in Europe)	Live viral vaccine produced from the modified vaccinia Ankara-Bavarian Nordic (MVA-BN strain)	Prevention of smallpox and Mpox disease in adults 18 years of age or older determined to be at high risk for smallpox or Mpox infection.	No major cutaneous reaction at the site of inoculation, no risk of inadvertent inoculation and autoinoculation.	Subcutaneously in two doses, 28 days apart.	[11,109,112]
ACAM2000®	Live vaccinia virus	Active immunization against smallpox disease for persons determined to be at high risk for smallpox infection, emergency access IND protocol for non-variola orthopoxvirus infection (e.g., Mpox) during an outbreak.	Major cutaneous reaction at the site of inoculation, risk of inadvertent inoculation and autoinoculation, eczema vaccinatum, progressive vaccinia, myopericarditis, post-vaccine encephalitis, inadvertent transmission, including vertical transmission resulting in fetal vaccinia.	Percutaneously by the multiple puncture technique in a single dose using a bifurcated needle.	[109,112]
Aventis Pasteur Smallpox Vaccine (APSV)	Investigational replication-competent vaccinia virus	Use in circumstances where ACAM2000® is depleted, not readily available, or in a case-by-case basis where ACAM2000® is contraindicated.	More commonly side effects including fatigue, rash, body ache, fever, itching and headache.	Administered by the same multiple puncture technique as ACAM2000®.	[112]
Antivirals					
Type	**Route**	**Mechanism of action**	**Major Side Effects**		**Ref.**
Tecovirimat	Oral Intravenous	Orthopoxvirus VP37 envelope wrapping protein inhibitor Inhibition of function of VP37 envelope protein	Nausea, vomiting, headache, abdominal pain, site reactions		[1,109]
Brincidofovir	Oral (Oral suspension, Tablets)	First, inhibition of DNA-polymerase mediated DNA synthesis. Second, acts as an acyclic nucleotide, incorporates into the viral DNA-chain and stops viral DNA-synthesis.	Nausea, diarrhea, vomiting, abdominal pain		[7,8,109]
Cidofovir	Intravenous	First, inhibition of viral replication by selectively inhibiting viral DNA-polymerases. Second, incorporates into viral DNA and inhibiting viral DNA-synthesis.	Fever, hypotony of eye, nephrotoxicity, iritis, uveitis, proteinuria, decrease serum bicarbonate, neutropenia, and infection		[12,109]
Immunotherapy					
Type	**Route**	**Mechanism of action**	**Major Side Effects**		**Ref.**
Vaccinia immune globulin	Intravenous	Human pooled-plasma antibodies from immunized-individuals with the smallpox vaccine which provide passive immunity	Dizziness, nausea, headache, rigors		[109,112,125]

Table 2
Contraindications for Nonemergency Use of ACAM2000® and JYNNEOS ®.

History or presence of atopic dermatitis
Other active exfoliative skin conditions (e.g., eczema, burns, impetigo, varicella zoster virus infection, herpes simplex virus infection, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease [keratosis follicularis])
Conditions associated with immunosuppression (e.g., human immunodeficiency virus [HIV] infection or acquired immune deficiency syndrome [AIDS], leukemia, lymphoma, generalized malignancy, solid organ transplantation, or therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor [TNF] inhibitors, or high-dose corticosteroids [≥2 mg/kg body weight or ≥ 20 mg/day of prednisone or its equivalent for ≥ 2 weeks], hematopoietic stem cell transplant recipients < 24 months post-transplant or ≥ 24 months, but who have graft-versus-host disease or disease relapse, or autoimmune disease [e.g. systemic lupus erythematosus] with immunodeficiency as a clinical component)
Persons aged < 1 year
Women who are pregnant or breastfeeding
Persons with a serious allergy to any component of ACAM2000®
Persons with known underlying heart disease with or without symptoms (e.g., coronary artery disease or cardiomyopathy)
Primary vaccinees with three or more known major cardiac risk factors (i.e., hypertension, diabetes, hypercholesterolemia, heart disease at age 50 years in a first-degree relative, and smoking)

from oral secretions, skin lesions, or resuspension of dried exudates without wearing appropriate protective gear. Exposure that is categorized as 1) high risk may also be determined by public health authorities based on unique circumstances, 2) intermediate-risk exposure involves being within six feet of an unmasked patient for three hours or more without wearing at least a surgical mask, or activities that result in contact between sleeves and the patient's skin or bodily fluids without wearing a gown, and 3) low-risk or uncertain exposure requires monitoring but does not warrant PoEP [112].

6.2. Treatments

6.2.1. Supportive treatment

The CDC guide's recommendations for controlling MPXV outbreaks state that most patients with mild symptoms recover without the need for medical intervention. The guide suggests that supportive measures, such as pain relief and hydration, are typically enough to ensure patients' comfort and care [113].

6.2.2. Antivirals

Several antiviral drugs may be effective in treating Mpox, although they were approved for smallpox treatment based on animal models (Table 1).

Tecovirimat is the first antiviral drug that has been approved for the treatment of smallpox in both adult and pediatric patients weighing at least 3 kg [114,115]. It is considered the preferred treatment option. The drug works by inhibiting the viral envelope protein VP37, which blocks the final stages of viral maturation and release from infected cells [109,116]. This mechanism ultimately hinders the spread of the virus within an infected cell. Although there is no clinical evidence to support Tecovirimat's efficacy against Mpox in humans, animal studies have demonstrated an increase in survival rates among Tecovirimat-treated animals with lethal Mpox infections compared to those who were given a placebo at various stages of the disease [117,118]. The Emergency Access Investigational New Protocol (EAINP) administered by the CDC permits the use of Tecovirimat for treating non-variola orthopoxvirus infections, including Mpox. Additionally, the protocol permits the opening of an oral capsule and mixing its contents with liquid or soft food for pediatric patients who weigh less than 13 kg. Tecovirimat is available in two formulations, an oral capsule and an intravenous vial, and is stocked in the Strategic National Stockpile (SNS) [114,115].

There are two additional antiviral drugs, Brincidofovir and Cidofovir, that have the potential to be effective in treating Mpox. Brincidofovir, which is an oral form of the intravenous drug Cidofovir, has been approved in the United States for treating smallpox since June 2021 [119]. The mechanism of action of these drugs involves inhibition of the viral DNA polymerase, which is a crucial enzyme required for viral DNA replication [120]. Although there is limited research on the use of Brincidofovir for treating Mpox in animal models, it has been found to be efficacious against orthopoxvirus infections [121,122]. While clinical data on Cidofovir's efficacy against Mpox in humans is lacking, studies have reported its in vitro activity and effectiveness in treating lethal Mpox infections in animals [123,124].

6.2.3. Vaccinia immune globulin (VIG)

Passive immunity can be conferred by antibodies derived from a combination of human plasma samples collected from individuals who have been vaccinated against smallpox [113]. The Food and Drug Administration (FDA) has authorized the use of VIG as a hyperimmune globulin to treat specific complications that arise from vaccinia vaccination, such as eczema vaccinatum and progressive vaccinia [125]. Although there is a lack of conclusive evidence on its efficacy against Mpox and smallpox, VIG may be prescribed for individuals with a history of exposure who suffer from severe immunodeficiency in T-cell function [126]. To ensure safe usage, treatment with VIG must be carried out under an IND application [113]. Consult Table 1 for a brief overview of these therapeutic agents.

6.3. Novel and innovative strategies against MPXV

Recent research has utilized proteomics and structural vaccinology to design mRNA and multi-epitope vaccines (MVC) against MPXV. In this study, ten MPXV proteins were identified as potential vaccine targets. Structural vaccinology approaches were used to map epitopes for B cells, CTLs, and helper T lymphocytes. These epitopes were combined with linkers to construct MVC and mRNA-based vaccines. Molecular docking and binding free energy calculations demonstrated robust interactions with TLR2 and efficient expression in E. coli K12. Immune simulation revealed that antigen levels peaked on the 5th day, with subsequent declines in antigen titer associated with the production of IgM, IgG, and other immune markers, suggesting the potential efficacy of the vaccine candidate in eliciting an immune response against MPXV [127].

In response to the ongoing monkeypox outbreak, addressing the virus's immune evasion mechanisms is crucial. One study tackled this challenge by employing structure-based drug design, binding free energy calculations, and molecular simulations to disrupt the F3L-dsRNA interaction. The study screened the African natural compound database and identified four compounds with docking scores ranging from − 6.35 to − 6.55 kcal/mol. Further validation through dissociation constant analysis, molecular dynamics simulations, and binding free energy calculations confirmed the pharmacological efficacy of these compounds against the F3L protein, highlighting their potential for developing novel therapeutics aimed at counteracting the immune evasion mechanisms of MPXV [99].

Furthermore, understanding MPXV pathogenesis is crucial for therapeutic development. Recent analyses of the S30L and D88N mutations, and their combination (S30L-D88N) in the G9R protein, reveal that these mutations alter interaction patterns with E4R but do not significantly impact binding affinity. Simulations show these mutations destabilize G9R and affect protein dynamics, though hydrogen bonding remains similar to wild-type G9R. The binding free energy for wild-type G9R

with E4R was −85.00 kcal/mol, compared to −42.75 kcal/mol, −43.68 kcal/mol, and −48.65 kcal/mol for the mutants. These results suggest that while the mutations do not directly affect G9R-E4R binding, they may influence broader aspects of MPXV pathogenesis [128].

Molecular screening and simulation studies have identified four compounds from the traditional Chinese medicines (TCM) database—TCM27763, TCM33057, TCM34450, and TCM31564—as potential inhibitors of the I7L protease from MPXV. These compounds demonstrated superior pharmacological potential compared to the control, TTP6171. They interact with key residues (Trp168, Asn171, Arg196, Cys237, Ser240, Trp242, Glu325, Ser326, and Cys328) of the protease, potentially impacting its function. Simulations showed that these TCM compounds formed stable complexes with the I7L protease, with tighter packing and reduced flexibility compared to the control. The average number of hydrogen bonds was higher for these compounds. Binding free energy calculations indicated more favorable interactions for the TCM compounds relative to the control [129].

Another study utilized advanced structure-based drug design, molecular simulation, and free energy calculations to uncover potential inhibitors targeting the thymidylate kinase (TMPK) of MPXV; this investigation explored a diverse array of compounds across several specialized databases: 1) TCM database: TCM26463, TCM2079, and TCM29893, 2) South African natural database: SANC00240, SANC00984, and SANC00986, 3) Natural Product Activity and Species Source database: NPC474409, NPC278434, and NPC158847, and 4) Collection of Open Natural Products database: CNP0404204, CNP0262936, and CNP0289137. Through comprehensive docking scores, simulation data, binding free energy evaluations, dissociation constants, and bioactivity assessments, these compounds demonstrated significant pharmacological activity against TMPK, indicating their potential efficacy in combating MPXV [130].

7. Conclusions and future trends

Mpox is a rare viral zoonotic disease caused by a double-stranded DNA virus belonging to the poxviridae family and orthopoxvirus genus, which causes symptoms similar to smallpox in humans. Lack of vaccination history against smallpox is a risk factor for developing Mpox. In the defense against Mpox, both innate and acquired immunity play a role. The present article primarily focuses on innate immunity against Mpox and explores various aspects of it. NK cells, DCs, and granulocytes play critical roles in innate immunity against poxviruses, particularly Mpox. TLRs and cytosolic DNA and RNA sensors also activate the production of type I IFNs, which prevents viral replication and facilitates antigen presentation and initiation of acquired immune responses. Since Mpox has re-emerged recently, understanding the mechanisms of innate immunity against it is crucial for developing effective therapeutic interventions to control its spread.

Future enhanced control strategies, ongoing research, and comprehensive studies are essential for improving public health responses to Mpox outbreaks. Further studies are necessary to understand the complexities of the immune response against poxviruses and identify potential therapeutic targets. Conducting randomized controlled trials to evaluate current treatment efficacy is also important. Given the significant impact of recent viral outbreaks, there is a pressing need for precise biosecurity and biosafety protocols, a better understanding of pathogen-host interactions, and stringent genomic surveillance. Despite ongoing threats, utilizing advanced technological tools and systematic efforts can help develop effective intervention strategies for future outbreaks.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this manuscript.

CRediT authorship contribution statement

Pouya Pashazadeh Azari: Writing – original draft. **Mohammad Rezaei Zadeh Rukerd:** Writing – review & editing, Supervision. **Javad Charostad:** Writing – review & editing, Supervision, Conceptualization. **Davood Bashash:** Visualization. **Niloofar Farsiu:** Writing – review & editing. **Saleh Behzadi:** Writing – review & editing. **Seyedeh Mahdieh Khoshnazar:** Visualization. **Sajjad Heydari:** Writing – review & editing. **Mohsen Nakhaie:** Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data are available from the corresponding author upon reasonable request.

Acknowledgements

None.

References

[1] E.J. Lefkowitz, C. Wang, C. Upton, Poxviruses: past, present and future, Virus Res. 117 (2006) 105–118, https://doi.org/10.1016/j.virusres.2006.01.016.
[2] J.G. Breman, Monkeypox: an Emerging Infection for Humans?, in: W. Michael Scheld, W.A. Craig, J.M. Hughes (Eds.), Emerg. Infect. 4, ASM Press, Washington, DC, USA, 2014: pp. 45–67. DOI: 10.1128/9781555816971.ch5.
[3] E. Petersen, A. Kantele, M. Koopmans, D. Asogun, A. Yinka-Ogunleye, C. Ihekweazu, A. Zumla, Human Monkeypox: Epidemiologic and Clinical Characteristics, Diagnosis, and Prevention, Infect. Dis. Clin. North Am. 33 (2019) 1027–1043, https://doi.org/10.1016/j.idc.2019.03.001.
[4] E. Alakunle, D. Kolawole, D. Diaz-Cánova, F. Alele, O. Adegboye, U. Moens, M. I. Okeke, A comprehensive review of monkeypox virus and mpox characteristics, Front. Cell. Infect. Microbiol. 14 (2024), https://doi.org/10.3389/fcimb.2024.1360586.
[5] J. Kaler, A. Hussain, G. Flores, S. Kheiri, D. Desrosiers, Monkeypox: A Comprehensive Review of Transmission, Pathogenesis, and Manifestation, Cureus (2022), https://doi.org/10.7759/cureus.26531.
[6] N.L. Bragazzi, J.D. Kong, N. Mahroum, C. Tsigalou, R. Khamisy-Farah, M. Converti, J. Wu, Epidemiological trends and clinical features of the ongoing monkeypox epidemic: A preliminary pooled data analysis and literature review, J. Med. Virol. (2022), https://doi.org/10.1002/jmv.27931.
[7] J.G. Breman, M.V. Kalisa-Ruti, E. Steniowski, A.I. Zanotto, I. Gromyko, Arita, Human monkeypox, 1970–79, Bull. World Health Organ. 58 (1980) 165–182.
[8] E.J. Tarín-Vicente, A. Alemany, M. Agud-Dios, M. Ubals, C. Suñer, A. Antón, M. Arando, J. Arroyo-Andrés, L. Calderón-Lozano, C. Casañ, J.M. Cabrera, P. Coll, V. Descalzo, M.D. Folgueira, J.N. García-Pérez, E. Gil-Cruz, B. González-Rodríguez, C. Gutiérrez-Collar, Á. Hernández-Rodríguez, P. López-Roa, M. de Los Ángeles Meléndez, J. Montero-Menárguez, I. Muñoz-Gallego, S.I. Palencia-Pérez, R. Paredes, A. Pérez-Rivilla, M. Piñana, N. Prat, A. Ramirez, Á. Rivero, C.A. Rubio-Muñiz, M. Vall, K.S. Acosta-Velásquez, A. Wang, C. Galván-Casas, M. Marks, P.L. Ortiz-Romero, O. Mitjà, Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study, Lancet Lond. Engl. 400 (2022) 661–669. DOI: 10.1016/S0140-6736(22)01436-2.
[9] C. Yu, Q. Wu, J. Xin, Q. Yu, Z. Ma, M. Xue, Q. Xu, C. Zheng, Designing a smallpox B-cell and T-cell multi-epitope subunit vaccine using a comprehensive immunoinformatics approach, Microbiol. Spectr. 12 (2024) e0046524.
[10] E.M. Bunge, B. Hoet, L. Chen, F. Lienert, H. Weidenthaler, L.R. Baer, R. Steffen, The changing epidemiology of human monkeypox—A potential threat? A systematic review, PLoS Negl. Trop. Dis. 16 (2022) e0010141.
[11] P.E.M. Fine, Z. Jezek, B. Grab, H. Dixon, The Transmission Potential of Monkeypox Virus in Human Populations, Int. J. Epidemiol. 17 (1988) 643–650, https://doi.org/10.1093/ije/17.3.643.
[12] A.M. McCollum, I.K. Damon, Human monkeypox, Clin. Infect. Dis. off. Publ. Infect. Dis. Soc. Am. 58 (2014) 260–267, https://doi.org/10.1093/cid/cit703.
[13] A.M. Likos, S.A. Sammons, V.A. Olson, A.M. Frace, Y. Li, M. Olsen-Rasmussen, W. Davidson, R. Galloway, M.L. Khristova, M.G. Reynolds, H. Zhao, D.S. Carroll, A. Curns, P. Formenty, J.J. Esposito, R.L. Regnery, I.K. Damon, A tale of two clades: monkeypox viruses, J. Gen. Virol. 86 (2005) 2661–2672, https://doi.org/10.1099/vir.0.81215-0.
[14] N. Chen, G. Li, M.K. Liszewski, J.P. Atkinson, P.B. Jahrling, Z. Feng, J. Schriewer, C. Buck, C. Wang, E.J. Lefkowitz, J.J. Esposito, T. Harms, I.K. Damon, R.L. Roper,

C. Upton, R.M.L. Buller, Virulence differences between monkeypox virus isolates from West Africa and the Congo basin, Virology 340 (2005) 46–63, https://doi.org/10.1016/j.virol.2005.05.030.
[15] E. Alakunle, U. Moens, G. Nchinda, M.I. Okeke, Monkeypox Virus in Nigeria: Infection Biology, Epidemiology, and Evolution, Viruses 12 (2020) 1257, https://doi.org/10.3390/v12111257.
[16] S. Elsayed, L. Bondy, W.P. Hanage, Monkeypox Virus Infections in Humans, Clin. Microbiol. Rev. 35 (2022) e00092–e00122.
[17] Y. Araf, J.F. Nipa, S. Naher, S.T. Maliha, H. Rahman, K.I. Arafat, M.R. Munif, M. J. Uddin, N. Jeba, S. Saha, J. Zhai, S.M.N. Hasan, M. Xue, M.G. Hossain, C. Zheng, Insights into the Transmission, Host Range, Genomics, Vaccination, and Current Epidemiology of the Monkeypox Virus, Vet. Med. Int. 2024 (2024) 8839830, https://doi.org/10.1155/2024/8839830.
[18] M. Nakhaie, Z. Pirmoradi, D. Bashash, M.R.Z. Rukerd, J. Charostad, Beyond skin deep: shedding light on the neuropsychiatric consequences of Monkeypox (Mpox), Acta Neurol. Belg. (2023), https://doi.org/10.1007/s13760-023-02361-4.
[19] A.S. Bhagavathula, J.E. Raubenheimer, A Real-Time Infodemiology Study on Public Interest in Mpox (Monkeypox) following the World Health Organization Global Public Health Emergency Declaration, Information 14 (2022) 5, https://doi.org/10.3390/info14010005.
[20] V.H. Sofiani, M.R.Z. Rukerd, J. Charostad, M. Pardeshenas, R. Ghazi, N. Arefinia, S. Shafieipour, F. Salajegheh, M. Nakhaie, From Entry to Evasion: A Comprehensive Analysis of Host-Virus Interactions for Monkeypox, Infect. Microbes Dis. 6 (2024) 56, https://doi.org/10.1097/IM9.0000000000000146.
[21] M.R.Z. Rukerd, P. Pourzand, N. Arefinia, D. Bashash, A. Sayyadi, M. Nakhaie, S.S. Meymandi, Monkeypox 2022 vs. COVID-19: a Review on a National Health Emergency with Emphasis on Cutaneous Manifestations, Curr. Infect. Dis. Rep. 25 (2023) 189–198. DOI: 10.1007/s11908-023-00813-9.
[22] Multi-country outbreak of mpox, External situation report#33- 31 May 2024, (n. d.). https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox–external-situation-report-33–31-may-2024 (accessed August 1, 2024).
[23] M.A. Zinnah, M.B. Uddin, T. Hasan, S. Das, F. Khatun, M.H. Hasan, R. Udonsom, M.M. Rahman, H.M. Ashour, The Re-Emergence of Mpox: Old Illness, Modern Challenges, Biomedicines 12 (2024) 1457, https://doi.org/10.3390/biomedicines12071457.
[24] S.A. Smith, G.J. Kotwal, Immune response to poxvirus infections in various animals, Crit. Rev. Microbiol. 28 (2002) 149–185, https://doi.org/10.1080/1040-840291046722.
[25] S. Li, Y. Xie, C. Yu, C. Zheng, Z. Xu, The battle between host antiviral innate immunity and immune evasion by cytomegalovirus, Cell. Mol. Life Sci. CMLS 81 (2024) 341, https://doi.org/10.1007/s00018-024-05369-y.
[26] H. Zhu, C. Zheng, The Race between Host Antiviral Innate Immunity and the Immune Evasion Strategies of Herpes Simplex Virus 1, Microbiol. Mol. Biol. Rev. MMBR 84 (2020) e00099–e00120, https://doi.org/10.1128/MMBR.00099-20.
[27] H. Li, Q.-Z. Huang, H. Zhang, Z.-X. Liu, X.-H. Chen, L.-L. Ye, Y. Luo, The landscape of immune response to monkeypox virus, EBioMedicine 87 (2023) 104424, https://doi.org/10.1016/j.ebiom.2022.104424.
[28] M. Zandi, M. Shafaati, F. Hosseini, Mechanisms of immune evasion of monkeypox virus, Front. Microbiol. 14 (2023) 1106247, https://doi.org/10.3389/fmicb.2023.1106247.
[29] H. Song, N. Josleyn, K. Janosko, J. Skinner, R.K. Reeves, M. Cohen, J. Blaney, P. Jahrling, Monkeypox virus infection of rhesus macaques induces massive expansion of NK cells, but suppresses NK cell function (P4369), Am Assoc Immnol, 2013.
[30] C.A. Biron, K.B. Nguyen, G.C. Pien, L.P. Cousens, T.P. Salazar-Mather, Natural killer cells in antiviral defense: function and regulation by innate cytokines, Annu. Rev. Immunol. 17 (1999) 189–220, https://doi.org/10.1146/annurev.immunol.17.1.189.
[31] J.A. Martinez, The Innate Immune Response to Vaccinia Viral Infection, (2010). https://dukespace.lib.duke.edu/dspace/handle/10161/2419 (accessed November 15, 2022).
[32] L.L. Lanier, NK cell recognition, Annu. Rev. Immunol. 23 (2005) 225–274.
[33] J.C. Ryan, C. Naper, S. Hayashi, M.R. Daws, Physiologic functions of activating natural killer (NK) complex-encoded receptors on NK cells, Immunol. Rev. 181 (2001) 126–137, https://doi.org/10.1034/j.1600-065x.2001.1810110.x.
[34] M. Bajénoff, B. Breart, A.Y.C. Huang, H. Qi, J. Cazareth, V.M. Braud, R. N. Germain, N. Glaichenhaus, Natural killer cell behavior in lymph nodes revealed by static and real-time imaging, J. Exp. Med. 203 (2006) 619–631, https://doi.org/10.1084/jem.20051474.
[35] M.B. Lodoen, L.L. Lanier, Natural killer cells as an initial defense against pathogens, Curr. Opin. Immunol. 18 (2006) 391–398, https://doi.org/10.1016/j.coi.2006.05.002.
[36] S.M. Vidal, S.I. Khakoo, C.A. Biron, Natural killer cell responses during viral infections: flexibility and conditioning of innate immunity by experience, Curr. Opin. Virol. 1 (2011) 497–512, https://doi.org/10.1016/j.coviro.2011.10.017.
[37] W.M. Yokoyama, S. Kim, A.R. French, The dynamic life of natural killer cells, Annu. Rev. Immunol. 22 (2004) 405–429, https://doi.org/10.1146/annurev.immunol.22.012703.104711.
[38] A. Martín-Fontecha, L.L. Thomsen, S. Brett, C. Gerard, M. Lipp, A. Lanzavecchia, F. Sallusto, Induced recruitment of NK cells to lymph nodes provides IFN-gamma for T(H)1 priming, Nat. Immunol. 5 (2004) 1260–1265, https://doi.org/10.1038/ni1138.
[39] B. Lowin, M.C. Peitsch, J. Tschopp, Perforin and granzymes: crucial effector molecules in cytolytic T lymphocyte and natural killer cell-mediated cytotoxicity, Curr. Top. Microbiol. Immunol. 198 (1995) 1–24, https://doi.org/10.1007/978-3-642-79414-8_1.
[40] M. Fang, M.T. Orr, P. Spee, T. Egebjerg, L.L. Lanier, L.J. Sigal, CD94 is essential for NK cell-mediated resistance to a lethal viral disease, Immunity 34 (2011) 579–589, https://doi.org/10.1016/j.immuni.2011.02.015.
[41] A. Al-Musa, J. Chou, B. LaBere, The resurgence of a neglected orthopoxvirus: Immunologic and clinical aspects of monkeypox virus infections over the past six decades, Clin. Immunol. Orlando Fla 243 (2022) 109108, https://doi.org/10.1016/j.clim.2022.109108.
[42] G. Abboud, V. Tahiliani, P. Desai, K. Varkoly, J. Driver, T.E. Hutchinson, S. Salek-Ardakani, Natural Killer Cells and Innate Interferon Gamma Participate in the Host Defense against Respiratory Vaccinia Virus Infection, J. Virol. 90 (2015) 129–141, https://doi.org/10.1128/JVI.01894-15.
[43] P.L. Earl, J.L. Americo, B. Moss, Insufficient Innate Immunity Contributes to the Susceptibility of the Castaneous Mouse to Orthopoxvirus Infection, J. Virol. 91 (2017) e01042–e01117, https://doi.org/10.1128/JVI.01042-17.
[44] P.L. Earl, J.L. Americo, B. Moss, Natural killer cells expanded in vivo or ex vivo with IL-15 overcomes the inherent susceptibility of CAST mice to lethal infection with orthopoxviruses, PLoS Pathog. 16 (2020) e1008505.
[45] C. Samuelsson, J. Hausmann, H. Lauterbach, M. Schmidt, S. Akira, H. Wagner, P. Chaplin, M. Suter, M. O'Keeffe, H. Hochrein, Survival of lethal poxvirus infection in mice depends on TLR9, and therapeutic vaccination provides protection, J. Clin. Invest. 118 (2008) 1776–1784, https://doi.org/10.1172/JCI33940.
[46] V. Tahiliani, G. Chaudhri, P. Eldi, G. Karupiah, The Orchestrated Functions of Innate Leukocytes and T Cell Subsets Contribute to Humoral Immunity, Virus Control, and Recovery from Secondary Poxvirus Challenge, J. Virol. 87 (2013) 3852–3861, https://doi.org/10.1128/JVI.03038-12.
[47] A. Chahroudi, D.A. Garber, P. Reeves, L. Liu, D. Kalman, M.B. Feinberg, Differences and Similarities in Viral Life Cycle Progression and Host Cell Physiology after Infection of Human Dendritic Cells with Modified Vaccinia Virus Ankara and Vaccinia Virus, J. Virol. 80 (2006) 8469–8481, https://doi.org/10.1128/JVI.02749-05.
[48] R. Drillien, D. Spehner, A. Bohbot, D. Hanau, Vaccinia virus-related events and phenotypic changes after infection of dendritic cells derived from human monocytes, Virology 268 (2000) 471–481, https://doi.org/10.1006/viro.2000.0203.
[49] M. Bossowska-Nowicka, M.B. Mielcarska, J. Struzik, A. Jackowska-Tracz, M. Tracz, K.P. Gregorczyk-Zboroch, M. Gieryńska, F.N. Toka, L. Szulc-Dąbrowska, Deficiency of Selected Cathepsins Does Not Affect the Inhibitory Action of ECTV on Immune Properties of Dendritic Cells, Immunol. Invest. 49 (2020) 232–248, https://doi.org/10.1080/08820139.2019.1631843.
[50] L.W. Kaminsky, J.J. Sei, N.J. Parekh, M.L. Davies, I.E. Reider, T.E. Krouse, C. C. Norbury, Redundant Function of Plasmacytoid and Conventional Dendritic Cells Is Required To Survive a Natural Virus Infection, J. Virol. 89 (2015) 9974–9985, https://doi.org/10.1128/JVI.01024-15.
[51] H. Fujisawa, Neutrophils play an essential role in cooperation with antibody in both protection against and recovery from pulmonary infection with influenza virus in mice, J. Virol. 82 (2008) 2772–2783, https://doi.org/10.1128/JVI.01210-07.
[52] G. McFadden, Poxvirus tropism, Nat. Rev. Microbiol. 3 (2005) 201–213, https://doi.org/10.1038/nrmicro1099.
[53] C. Zheng, Evasion of Cytosolic DNA-Stimulated Innate Immune Responses by Herpes Simplex Virus 1, J. Virol. 92 (2018) e00099–e00117, https://doi.org/10.1128/JVI.00099-17.
[54] C. Su, G. Zhan, C. Zheng, Evasion of host antiviral innate immunity by HSV-1, an update, Virol. J. 13 (2016) 38, https://doi.org/10.1186/s12985-016-0495-5.
[55] A. Murira, A. Lamarre, Type-I Interferon Responses: From Friend to Foe in the Battle against Chronic Viral Infection, Front. Immunol. 7 (2016) 609, https://doi.org/10.3389/fimmu.2016.00609.
[56] S.C. Johnston, K.L. Lin, J.H. Connor, G. Ruthel, A. Goff, L.E. Hensley, In vitro inhibition of monkeypox virus production and spread by Interferon-β, Virol. J. 9 (2012) 5, https://doi.org/10.1186/1743-422X-9-5.
[57] M. Matsumoto, T. Seya, TLR3: interferon induction by double-stranded RNA including poly(I:C), Adv. Drug Deliv. Rev. 60 (2008) 805–812, https://doi.org/10.1016/j.addr.2007.11.005.
[58] H.-L. Eng, Y.-Y. Hsu, T.-M. Lin, Differences in TLR7/8 activation between monocytes and macrophages, Biochem. Biophys. Res. Commun. 497 (2018) 319–325, https://doi.org/10.1016/j.bbrc.2018.02.079.
[59] C. Wilkins, M. Gale, Recognition of viruses by cytoplasmic sensors, Curr. Opin. Immunol. 22 (2010) 41–47, https://doi.org/10.1016/j.coi.2009.12.003.
[60] E.Y. Lee, C. Zhang, J. Di Domizio, F. Jin, W. Connell, M. Hung, N. Malkoff, V. Veksler, M. Gilliet, P. Ren, G.C.L. Wong, Helical antimicrobial peptides assemble into protofibril scaffolds that present ordered dsDNA to TLR9, Nat. Commun. 10 (2019) 1012, https://doi.org/10.1038/s41467-019-08868-w.
[61] D.B. Sutherland, C. Ranasinghe, M. Regner, S. Phipps, K.I. Matthaei, S.L. Day, I. A. Ramshaw, Evaluating vaccinia virus cytokine co-expression in TLR GKO mice, Immunol. Cell Biol. 89 (2011) 706–715, https://doi.org/10.1038/icb.2010.157.
[62] J. Martinez, X. Huang, Y. Yang, Toll-like receptor 8-mediated activation of murine plasmacytoid dendritic cells by vaccinia viral DNA, Proc. Natl. Acad. Sci. 107 (2010) 6442–6447, https://doi.org/10.1073/pnas.0913291107.
[63] A.G. Dias Junior, N.G. Sampaio, J. Rehwinkel, A Balancing Act: MDA5 in Antiviral Immunity and Autoinflammation, Trends Microbiol. 27 (2019) 75–85, https://doi.org/10.1016/j.tim.2018.08.007.

[64] R.F. Boone, R.P. Parr, B. Moss, Intermolecular duplexes formed from polyadenylylated vaccinia virus RNA, J. Virol. 30 (1979) 365–374, https://doi.org/10.1128/JVI.30.1.365-374.1979.
[65] A. Decout, J.D. Katz, S. Venkatraman, A. Ablasser, The cGAS–STING pathway as a therapeutic target in inflammatory diseases, Nat. Rev. Immunol. 21 (2021) 548–569, https://doi.org/10.1038/s41577-021-00524-z.
[66] Y. Lin, C. Zheng, A Tug of War: DNA-Sensing Antiviral Innate Immunity and Herpes Simplex Virus Type I Infection, Front. Microbiol. 10 (2019) 2627, https://doi.org/10.3389/fmicb.2019.02627.
[67] M. El-Jesr, M. Teir, C. Maluquer de Motes, Vaccinia Virus Activation and Antagonism of Cytosolic DNA Sensing, Front. Immunol. 11 (2020) 568412, https://doi.org/10.3389/fimmu.2020.568412.
[68] G. Chen, S. Chen, X. Chen, Role of complement and perspectives for intervention in transplantation, Immunobiology 218 (2013) 817–827, https://doi.org/10.1016/j.imbio.2012.09.002.
[69] E.A. Uvarova, A.V. Totmenin, L.S. Sandakhchiev, S.N. Shchelkunov, The gene of the complement-binding protein, an important anti-inflammatory factor of orthopoxviruses, is deleted from the genome of Western African strains of monkeypox virus, Dokl. Biochem. Biophys. 400 (2005) 14–16, https://doi.org/10.1007/s10628-005-0021-y.
[70] E. Ciulla, A. Emery, D. Konz, J. Krushkal, Evolutionary history of orthopoxvirus proteins similar to human complement regulators, Gene 355 (2005) 40–47, https://doi.org/10.1016/j.gene.2005.05.008.
[71] D.J. Doorduijn, B.W. Bardoel, D.A.C. Heesterbeek, M. Ruyken, G. Benn, E. S. Parsons, B.W. Hoogenboom, S.H.M. Rooijakkers, Bacterial killing by complement requires direct anchoring of membrane attack complex precursor C5b–7, PLOS Pathog. 16 (2020) e1008606.
[72] R.D. Estep, I. Messaoudi, M.A. O'Connor, H. Li, J. Sprague, A. Barron, F. Engelmann, B. Yen, M.F. Powers, J.M. Jones, B.A. Robinson, B. U. Orzechowska, M. Manoharan, A. Legasse, S. Planer, J. Wilk, M.K. Axthelm, S. W. Wong, Deletion of the Monkeypox Virus Inhibitor of Complement Enzymes Locus Impacts the Adaptive Immune Response to Monkeypox Virus in a Nonhuman Primate Model of Infection, J. Virol. 85 (2011) 9527–9542, https://doi.org/10.1128/JVI.00199-11.
[73] G.J. Kotwal, A.W. Hügin, B. Moss, Mapping and insertional mutagenesis of a vaccinia virus gene encoding a 13,800-Da secreted protein, Virology 171 (1989) 579–587, https://doi.org/10.1016/0042-6822(89)90627-2.
[74] M. Barry, S. Hnatiuk, K. Mossman, S.F. Lee, L. Boshkov, G. McFadden, The myxoma virus M-T4 gene encodes a novel RDEL-containing protein that is retained within the endoplasmic reticulum and is important for the productive infection of lymphocytes, Virology 239 (1997) 360–377, https://doi.org/10.1006/viro.1997.8894.
[75] G.J. Kotwal, Poxviral mimicry of complement and chemokine system components: what's the end game? Immunol. Today 21 (2000) 242–248, https://doi.org/10.1016/S0167-5699(00)01606-6.
[76] A.M. Rosengard, Y. Liu, Z. Nie, R. Jimenez, Variola virus immune evasion design: expression of a highly efficient inhibitor of human complement, Proc. Natl. Acad. Sci. u. s. a. 99 (2002) 8808–8813, https://doi.org/10.1073/pnas.112220499.
[77] E.A. Uvarova, S.N. Shchelkunov, Species-specific differences in the structure of orthopoxvirus complement-binding protein, Virus Res. 81 (2001) 39–45, https://doi.org/10.1016/S0168-1702(01)00332-X.
[78] A. Herbert, J. O'leary, M. Krych-Goldberg, J.P. Atkinson, P.N. Barlow, Three-dimensional structure and flexibility of proteins of the RCA family—a progress report, Biochem. Soc. Trans. 30 (2002) 990–996.
[79] S.A. Smith, N.P. Mullin, J. Parkinson, S.N. Shchelkunov, A.V. Totmenin, V. N. Loparev, R. Srisatjaluk, D.N. Reynolds, K.L. Keeling, D.E. Justus, P.N. Barlow, G.J. Kotwal, Conserved Surface-Exposed K/R-X-K/R Motifs and Net Positive Charge on Poxvirus Complement Control Proteins Serve as Putative Heparin Binding Sites and Contribute to Inhibition of Molecular Interactions with Human Endothelial Cells: a Novel Mechanism for Evasion of Host Defense, J. Virol. 74 (2000) 5659–5666, https://doi.org/10.1128/JVI.74.12.5659-5666.2000.
[80] S.N. Isaacs, G.J. Kotwal, B. Moss, Vaccinia virus complement-control protein prevents antibody-dependent complement-enhanced neutralization of infectivity and contributes to virulence, Proc. Natl. Acad. Sci. 89 (1992) 628–632.
[81] G.J. Kotwal, B. Moss, Vaccinia virus encodes a secretory polypeptide structurally related to complement control proteins, Nature 335 (1988) 176–178.
[82] R. McKenzie, G.J. Kotwal, B. Moss, C.H. Hammer, M.M. Frank, Regulation of complement activity by vaccinia virus complement-control protein, J. Infect. Dis. 166 (1992) 1245–1250.
[83] A. Sahu, S.N. Isaacs, A.M. Soulika, J.D. Lambris, Interaction of vaccinia virus complement control protein with human complement proteins: factor I-mediated degradation of C3b to iC3b1 inactivates the alternative complement pathway, J. Immunol. 160 (1998) 5596–5604.
[84] J.R. Weaver, S.N. Isaacs, Monkeypox virus and insights into its immunomodulatory proteins, Immunol. Rev. 225 (2008) 96–113, https://doi.org/10.1111/j.1600-065X.2008.00691.x.
[85] P.N. Hudson, J. Self, S. Weiss, Z. Braden, Y. Xiao, N.M. Girgis, G. Emerson, C. Hughes, S.A. Sammons, S.N. Isaacs, I.K. Damon, V.A. Olson, Elucidating the Role of the Complement Control Protein in Monkeypox Pathogenicity, PLoS ONE 7 (2012) e35086.
[86] M.K. Liszewski, J.P. Atkinson, Membrane cofactor protein (CD46) and decay-accelerating factor (CD55), Complement Syst. K Rother GO Till GM Hansch Ed. Springer Velag Berl. Heidelb. (1998) 146–162.
[87] P. Agrawal, S. Sharma, P. Pal, H. Ojha, J. Mullick, A. Sahu, The imitation game: a viral strategy to subvert the complement system, FEBS Lett. 594 (2020) 2518–2542, https://doi.org/10.1002/1873-3468.13856.
[88] W.D. Arndt, S. Cotsmire, K. Trainor, H. Harrington, K. Hauns, K.V. Kibler, T. P. Huynh, B.L. Jacobs, Evasion of the Innate Immune Type I Interferon System by Monkeypox Virus, J. Virol. 89 (2015) 10489–10499, https://doi.org/10.1128/JVI.00304-15.
[89] C. Park, C. Peng, M.J. Rahman, S.L. Haller, L. Tazi, G. Brennan, S. Rothenburg, Orthopoxvirus K3 orthologs show virus- and host-specific inhibition of the antiviral protein kinase PKR, PLOS Pathog. 17 (2021) e1009183.
[90] M.A. García, J. Gil, I. Ventoso, S. Guerra, E. Domingo, C. Rivas, M. Esteban, Impact of Protein Kinase PKR in Cell Biology: from Antiviral to Antiproliferative Action, Microbiol. Mol. Biol. Rev. 70 (2006) 1032–1060, https://doi.org/10.1128/MMBR.00027-06.
[91] P. Zhang, C.E. Samuel, Induction of Protein Kinase PKR-dependent Activation of Interferon Regulatory Factor 3 by Vaccinia Virus Occurs through Adapter IPS-1 Signaling, J. Biol. Chem. 283 (2008) 34580–34587, https://doi.org/10.1074/jbc.M807029200.
[92] H. Yu, R.C. Bruneau, G. Brennan, S. Rothenburg, Battle Royale: Innate Recognition of Poxviruses and Viral Immune Evasion, Biomedicines 9 (2021) 765, https://doi.org/10.3390/biomedicines9070765.
[93] H. Koehler, S. Cotsmire, T. Zhang, S. Balachandran, J.W. Upton, J. Langland, D. Kalman, B.L. Jacobs, E.S. Mocarski, Vaccinia virus E3 prevents sensing of Z-RNA to block ZBP1-dependent necroptosis, Cell Host Microbe 29 (2021) 1266–1276.e5, https://doi.org/10.1016/j.chom.2021.05.009.
[94] H.W. Chang, B.L. Jacobs, Identification of a conserved motif that is necessary for binding of the vaccinia virus E3L gene products to double-stranded RNA, Virology 194 (1993) 537–547, https://doi.org/10.1006/viro.1993.1292.
[95] J.O. Langland, B.L. Jacobs, The role of the PKR-inhibitory genes, E3L and K3L, in determining vaccinia virus host range, Virology 299 (2002) 133–141, https://doi.org/10.1006/viro.2002.1479.
[96] T. Brandt, M.C. Heck, S. Vijaysri, G.M. Jentarra, J.M. Cameron, B.L. Jacobs, The N-terminal domain of the vaccinia virus E3L-protein is required for neurovirulence, but not induction of a protective immune response, Virology 333 (2005) 263–270, https://doi.org/10.1016/j.virol.2005.01.006.
[97] J.O. Langland, B.L. Jacobs, Inhibition of PKR by vaccinia virus: role of the N- and C-terminal domains of E3L, Virology 324 (2004) 419–429, https://doi.org/10.1016/j.virol.2004.03.012.
[98] T.A. Brandt, B.L. Jacobs, Both carboxy- and amino-terminal domains of the vaccinia virus interferon resistance gene, E3L, are required for pathogenesis in a mouse model, J. Virol. 75 (2001) 850–856, https://doi.org/10.1128/JVI.75.2.850-856.2001.
[99] M. Suleman, T. Ahmad, K. Shah, N.A. Albekairi, A. Alshammari, A. Khan, D.-Q. Wei, H.M. Yassine, S. Crovella, Exploring the natural products chemical space to abrogate the F3L-dsRNA interface of monkeypox virus to enhance the immune responses using molecular screening and free energy calculations, Front. Pharmacol. 14 (2023) 1328308, https://doi.org/10.3389/fphar.2023.1328308.
[100] W.D. Arndt, S.D. White, B.P. Johnson, T. Huynh, J. Liao, H. Harrington, S. Cotsmire, K.V. Kibler, J. Langland, B.L. Jacobs, Monkeypox virus induces the synthesis of less dsRNA than vaccinia virus, and is more resistant to the anti-poxvirus drug, IBT, than vaccinia virus, Virology 497 (2016) 125–135, https://doi.org/10.1016/j.virol.2016.07.016.
[101] N. Meade, C. Furey, H. Li, R. Verma, Q. Chai, M.G. Rollins, S. DiGiuseppe, M. H. Naghavi, D. Walsh, Poxviruses Evade Cytosolic Sensing through Disruption of an mTORC1-mTORC2 Regulatory Circuit, Cell 174 (2018) 1143–1157.e17, https://doi.org/10.1016/j.cell.2018.06.053.
[102] H. Harapan, Y. Ophinni, D. Megawati, A. Frediansyah, S.S. Mamada, M. Salampe, T. Bin Emran, W. Winardi, R. Fathima, S. Sirinam, P. Sittikul, A.M. Stoian, F. Nainu, M. Sallam, Monkeypox: A Comprehensive Review, Viruses 14 (2022) 2155. DOI: 10.3390/v14102155.
[103] M. Altindis, E. Puca, L. Shapo, Diagnosis of monkeypox virus - An overview, Travel Med. Infect. Dis. 50 (2022) 102459, https://doi.org/10.1016/j.tmaid.2022.102459.
[104] A. Lawrence, J. Anejo-Okopi, B. Adeseye, The Feasibility of Elimination of Monkeypox Virus in Nigeria: A Systematic Review, Cureus 16 (2024) e61867.
[105] Y. Huang, L. Mu, W. Wang, Monkeypox: epidemiology, pathogenesis, treatment and prevention, Signal Transduct. Target. Ther. 7 (2022) 373, https://doi.org/10.1038/s41392-022-01215-4.
[106] J. Lu, H. Xing, C. Wang, M. Tang, C. Wu, F. Ye, L. Yin, Y. Yang, W. Tan, L. Shen, Mpox (formerly monkeypox): pathogenesis, prevention, and treatment, Signal Transduct. Target. Ther. 8 (2023) 458, https://doi.org/10.1038/s41392-023-01675-2.
[107] D.L. Heymann, M. Szczeniowski, K. Esteves, Re-emergence of monkeypox in Africa: a review of the past six years, Br. Med. Bull. 54 (1998) 693–702.
[108] E. Hammarlund, M.W. Lewis, S.V. Carter, I. Amanna, S.G. Hansen, L.I. Strelow, S. W. Wong, P. Yoshihara, J.M. Hanifin, M.K. Slifka, Multiple diagnostic techniques identify previously vaccinated individuals with protective immunity against monkeypox, Nat. Med. 11 (2005) 1005–1011.
[109] S. Ghafari, M.R.Z. Rukerd, D. Bashash, M. Nakhaie, J. Charostad, M. Zarei, A. Dehghani, Anti-Monkeypox Infection Approaches: From Prevention to Therapeutic Lines, Clin. Pharmacol. Drug Dev. (2023), https://doi.org/10.1002/cpdd.1275.
[110] B.W. Petersen, T.J. Harms, M.G. Reynolds, L.H. Harrison, Use of Vaccinia Virus Smallpox Vaccine in Laboratory and Health Care Personnel at Risk for Occupational Exposure to Orthopoxviruses - Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR Morb, Mortal. Wkly. Rep. 65 (2016) (2015) 257–262, https://doi.org/10.15585/mmwr.mm6510a2.
[111] S. Chakraborty, R.K. Mohapatra, D. Chandran, M. Alagawany, P. Sv, M.A. Islam, C. Chakraborty, K. Dhama, Monkeypox vaccines and vaccination strategies:

Current knowledge and advances. An update – Correspondence, Int. J. Surg. 105 (2022) 106869. DOI: 10.1016/j.ijsu.2022.106869.
[112] CDC, Mpox in the U.S., Cent. Dis. Control Prev. (2022). https://www.cdc.gov/poxvirus/monkeypox/prevention/index.html (accessed February 10, 2023).
[113] J.G. Rizk, G. Lippi, B.M. Henry, D.N. Forthal, Y. Rizk, Prevention and Treatment of Monkeypox, Drugs 82 (2022) 957–963, https://doi.org/10.1007/s40265-022-01742-y.
[114] M. Merchlinsky, A. Albright, V. Olson, H. Schiltz, T. Merkeley, C. Hughes, B. Petersen, M. Challberg, The development and approval of tecoviromat (TPOXX®), the first antiviral against smallpox, Antiviral Res. 168 (2019) 168–174, https://doi.org/10.1016/j.antiviral.2019.06.005.
[115] S.M. Hoy, Tecovirimat: First Global Approval, Drugs 78 (2018) 1377–1382, https://doi.org/10.1007/s40265-018-0967-6.
[116] A.T. Russo, D.W. Grosenbach, J. Chinsangaram, K.M. Honeychurch, P.G. Long, C. Lovejoy, B. Maiti, I. Meara, D.E. Hruby, An overview of tecovirimat for smallpox treatment and expanded anti-orthopoxvirus applications, Expert Rev. Anti Infect. Ther. 19 (2021) 331–344.
[117] D.C. Quenelle, R.M.L. Buller, S. Parker, K.A. Keith, D.E. Hruby, R. Jordan, E. R. Kern, Efficacy of delayed treatment with ST-246 given orally against systemic orthopoxvirus infections in mice, Antimicrob. Agents Chemother. 51 (2007) 689–695.
[118] D.W. Grosenbach, K. Honeychurch, E.A. Rose, J. Chinsangaram, A. Frimm, B. Maiti, C. Lovejoy, I. Meara, P. Long, D.E. Hruby, Oral tecovirimat for the treatment of smallpox, N. Engl. J. Med. 379 (2018) 44–53.
[119] C. for D.E. and Research, FDA approves drug to treat smallpox, FDA (2021). https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-treat-smallpox (accessed February 9, 2023).
[120] R. Lanier, L. Trost, T. Tippin, B. Lampert, A. Robertson, S. Foster, M. Rose, W. Painter, R. O'Mahony, M. Almond, Development of CMX001 for the treatment of poxvirus infections, Viruses 2 (2010) 2740–2762.
[121] S. Parker, N.G. Chen, S. Foster, H. Hartzler, E. Hembrador, D. Hruby, R. Jordan, R. Lanier, G. Painter, W. Painter, Evaluation of disease and viral biomarkers as triggers for therapeutic intervention in respiratory mousepox–an animal model of smallpox, Antiviral Res. 94 (2012) 44–53.
[122] A.D. Rice, M.M. Adams, G. Wallace, A.M. Burrage, S.F. Lindsey, A.J. Smith, D. Swetnam, B.R. Manning, S.A. Gray, B. Lampert, Efficacy of CMX001 as a post exposure antiviral in New Zealand White rabbits infected with rabbitpox virus, a model for orthopoxvirus infections of humans, Viruses 3 (2011) 47–62.
[123] E.J. Baker, G.A. Lee, A Retrospective Observational Study Examining the Effect of Thoracic Epidural and Patient Controlled Analgesia on Short-term Outcomes in Blunt Thoracic Trauma Injuries, Medicine (baltimore) 95 (2016) e2374.
[124] D.F. Smee, Progress in the discovery of compounds inhibiting orthopoxviruses in animal models, Antivir. Chem. Chemother. 19 (2008) 115–124.
[125] R. Wittek, Vaccinia immune globulin: current policies, preparedness, and product safety and efficacy, Int. J. Infect. Dis. 10 (2006) 193–201.
[126] R.A. Weinstein, A. Nalca, A.W. Rimoin, S. Bavari, C.A. Whitehouse, Reemergence of monkeypox: prevalence, diagnostics, and countermeasures, Clin. Infect. Dis. 41 (2005) 1765–1771.
[127] Y. Jin, A. Fayyaz, A. Liaqat, A. Khan, A. Alshammari, Y. Wang, R.-X. Gu, D.-Q. Wei, Proteomics-based vaccine targets annotation and design of subunit and mRNA-based vaccines for Monkeypox virus (MPXV) against the recent outbreak, Comput. Biol. Med. 159 (2023) 106893, https://doi.org/10.1016/j.compbiomed.2023.106893.
[128] Y. Jin, S.J. Asad Gillani, F. Batool, F.M. Alshabrmi, E.A. Alatawi, Y. Waheed, A. Mohammad, A. Khan, D.-Q. Wei, Structural and molecular investigation of the impact of S30L and D88N substitutions in G9R protein on coupling with E4R from Monkeypox virus (MPXV), J. Biomol. Struct. Dyn. (2024) 1–12. DOI: 10.1080/07391102.2023.2291159.
[129] A. Khan, M. Shahab, F. Nasir, Y. Waheed, A. Alshammari, A. Mohammad, G. Zichen, R. Li, D.Q. Wei, Exploring the Traditional Chinese Medicine (TCM) database chemical space to target I7L protease from monkeypox virus using molecular screening and simulation approaches, SAR QSAR Environ. Res. 34 (2023) 689–708, https://doi.org/10.1080/1062936X.2023.2250723.
[130] A. Khan, S. Adil, H.A. Qudsia, Y. Waheed, F.M. Alshabrmi, D.-Q. Wei, Structure-based design of promising natural products to inhibit thymidylate kinase from Monkeypox virus and validation using free energy calculations, Comput. Biol. Med. 158 (2023) 106797, https://doi.org/10.1016/j.compbiomed.2023.106797.