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Innate Immune Response to Monkeypox Virus Infection: Mechanisms and Immune Escape

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Abstract
Background: The reemergence of monkeypox virus (Mpox, formerly monkeypox) in 2022 in non-endemic countries has raised significant concerns for global health due to its high transmissibility and mortality rate. A major challenge in combating Mpox is its ability to evade the host's innate immune system, the first line of defense against viral infections. ***Summary:*** Mpox encodes various proteins that interfere with key antiviral pathways and mechanisms, such as the nuclear factor kappa B signaling, cytokine production, complement and inflammasome activation, and chemokine binding. These proteins modulate the expression and function of innate immune mediators, such as interferons, interleukins, and Toll-like receptors, and impair the recruitment and activation of innate immune cells, such as natural killer cells. By suppressing or altering these innate immune responses, Mpox enhances its replication and infection in the host tissues and organs, leading to systemic inflammation, tissue damage, and organ failure. ***Key Messages:*** This study reveals new insights into the molecular and cellular interactions between Mpox and the host's innate immune system. It identifies potential targets and strategies for antiviral interventions, highlighting the importance of understanding these interactions to develop effective treatments and improve global health responses to Mpox outbreaks.

Introduction

Monkeypox virus (Mpox) is one of the DNA viruses that are classified in the genus Orthopoxviruses. This virus is closely related to the variola virus that causes smallpox. This disease appears with significant differences compared to smallpox. For example, contracting Mpox is associated with symptoms such as skin rashes, fever, and swelling of the lymph nodes, which are also present in smallpox, but with the difference that they are milder in Mpox. In 2022, the reemergence of Mpox in Europe and North America reignited concerns about its pathogenicity [1–4]. This virus can be transmitted in different ways, but the most common mode is through

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close contact with infected people. Physical contact with infected animals, especially through bites, scratches, or handling their tissues, can also increase the risk of infection. Additionally, transmission can occur through respiratory droplets, direct contact with body fluids or waste, or contact with contaminated objects such as bedding or clothing [5, 6].

In orthopoxvirus infections, including Mpox, immune evasion plays a significant role in the development of the disease. The virus produces proteins that disrupt the host's natural antiviral defenses, such as nuclear factor kappa B (NF-κB) signaling and cytokine production. Despite the innate immune system acting as the primary defense against viruses, Mpox has evolved strategies to circumvent these defenses, establishing infection [7, 8].

This review will explore the various innate immune pathways triggered by Mpox and how the virus manipulates these responses to cause disease. Additionally, we will discuss the innate immune response in the context of immunocompromised patients confronting Mpox. Understanding these mechanisms can guide future research into Mpox therapies, improving treatment strategies and patient outcomes.

The Interface between Host Immunity and Mpox

The innate immune system is the first line of defense against Mpox infection. Innate immune cells like monocytes and natural killer (NK) cells play a critical role by producing type I interferons (IFNs) and inflammatory cytokines. However, the Mpox can suppress the cytotoxicity and motility of NK cells. The mucosal tissues are the main site of Mpox infection, and increased production of mucosal immune components like calcium-binding proteins has been observed in Mpox-infected primates. Mpox infection elicits a prominent Th2 immune response with elevated levels of Th2-associated cytokines (IL-4, IL-5, IL-6, IL-10), while Th1-associated cytokines (IL-2, IL-12, TNF-α, IFN-γ) remain within the normal range, indicating the complex immune dysregulation during Mpox infection [9–11].

Adaptive immunity, particularly the antibody response, plays a critical role in clearing the Mpox. Mpox-specific immunoglobulin G and immunoglobulin M antibodies are widely detected in infected patients and used as diagnostic markers. B cells are essential for the protection conferred by Mpox vaccination. T cells also participate in the protective response against Mpox, as T cell responses to Mpox have been observed in healthy individuals, especially those born before 1976 who likely received the smallpox vaccine, which provides cross-protection against Mpox [12, 13].

Several factors influence the immune response to Mpox disease. Individuals with a history of smallpox are more resistant to Mpox due to the similarity between the viruses and the existence of cross-immunity, resulting in a stronger genetic background and immune response. Younger individuals typically exhibit a more robust immune response to the Mpox, as the immune system weakens with age [14, 15]. However, immunocompromised individuals, such as those with human immunodeficiency virus, cancer, and organ transplant recipients, are at a higher risk of contracting Mpox and may experience longer recovery periods. Their compromised immune status hampers their bodies' ability to effectively combat the Mpox virus [16].

Innate Immune Signaling Pathway to Mpox

The innate immune signaling pathway has a significant impact on the occurrence of the immune system responses and fight against infections. In addition, dendritic cells (DCs) are also activated together with macrophages to perform antiviral activities. The immune system primarily depends on pattern recognition receptor (PRRs) to recognize viruses [17, 18]. PRRs are proteins expressed by immune cells that can recognize specific molecular patterns associated with pathogens, including viruses. One of the important classes of PRRs that play a role in viral particle recognition is Toll-like receptor (TLRs). TLRs have the ability to recognize different parts of viruses [19]. For example, they can detect viral nucleic acids including DNA or RNA or viral proteins [20, 21]. Innate immune cells initiate their activity with a signaling cascade. By doing this, molecules called cytokines are released, which are among the pro-inflammatory molecules. The signaling pathways activated by PRRs depend on the receptor and the type of virus it encounters [22–24]. One of the pathways studied is the TLR signaling pathway, which includes a series of protein interactions and phosphorylation events. This pathway includes various functions, the most important of which is the stimulation of some important factors in transcription. Some of these factors include IFN regulatory factor 3 (IRF3) and NF-κB (Fig. 1) [25].

After these crucial transcriptional factors are activated, IFNs and some cytokines are produced [26]. Type I IFNs, including interferon-alpha (IFN-α) and interferon-beta (IFN-β), have potent antiviral properties that induce an antiviral state in lateral cells and render them resistant to viral replication [27]. Type I IFNs activate NK cells by their actions. They also increase the production of

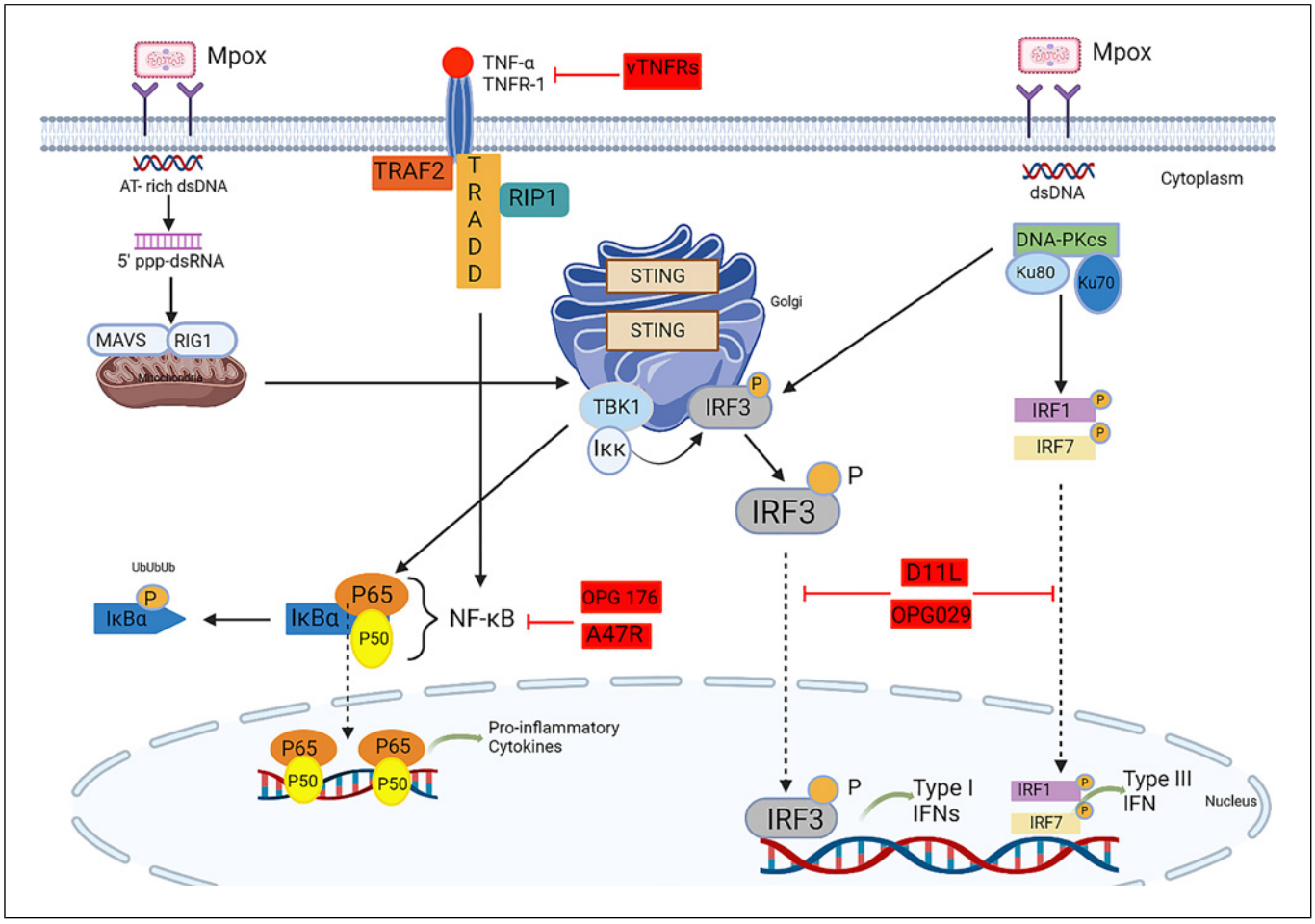

Fig. 1. Activation and inhibition of cytosolic DNA sensors by Mpox infection. Cytosolic DNA sensors (CDSs) detect double-stranded DNA (dsDNA) in the cytoplasm and trigger NF-κB and IRF3/IRF7 signaling pathways, leading to the production of pro-inflammatory cytokines, type I interferons (IFN I) and type III interferons (IFN III) to combat viral infection. Mpox encodes proteins that interfere with these pathways, such as A47R and OPG176, which inhibit NF-κB activation, and D11L and OPG029, which inhibit IRF3 and IRF7 activation. Mpox also secretes viral TNF receptor (TNFR) orthologs that compete with cellular TNFRs for binding to TNF, thereby blocking its inflammatory and apoptotic effects. The various Mpox inhibitors are shown in red boxes. IRF1/3/7, interferon regulatory factor 1/3/7; IκB, inhibitor κBα; MAVS, mitochondrial antiviral-signaling protein; STING, stimulator of interferon genes; NF-κB, nuclear factor kappa B; RIG-I, retinoic acid-inducible gene I; TBK1, TRAF family member-associated NF-κB activator (TANK)-binding kinase 1; TNF, tumor necrosis factor-alpha; TRADD, tumor necrosis factor receptor type 1-associated DEATH domain protein; TRAF, tumor necrosis factor receptor-associated factor.

cytotoxic T lymphocytes. The occurrence of such reactions is necessary for a proper and effective fight against viruses. In addition, the innate immune system can activate the pathway and thereby prevent the spread of the virus. This is done through the activation of caspases, which are proteases involved in cell death processes [28, 29].

Although Mpox was identified decades ago, the human immune system has yet to develop an adequate response against it. Currently, there is not enough information and required research on the ways in which Mpox evades the immune mechanisms. For this reason, findings from research on vaccinia virus (VACV) and other orthopoxviruses can be considered as a reference for research between Mpox and the human immune systems [30]. Many researches have been conducted on these viruses and their pathogenic mechanisms and have shown that Mpox has many structural and functional similarities with other orthopoxviruses. For this reason, the interaction of Mpox with the human immune system is inferred from studies conducted on VACV [30–32].

Mammalian cells have developed PRRs to detect microbial pathogens, including viral nucleic acids. Upon recognition, PRRs initiate signaling cascades that lead to the activation of immune transcription factors and the production of molecules involved in immune responses. PRRs can stimulate signaling pathways involving host cofactors such as myeloid differentiation primary response 88, Translocating chain-associating membrane protein (TRAM), TIR domain-containing adapter protein (TIRAP), and TIR domain-containing adapter inducing IFN-β (TRIF). Activation of these cofactors leads to the activation of important immune transcription factors, including NF-κB and IRFs. NF-κB stimulates the production of pro-inflammatory molecules, while IRFs are involved in the production of antiviral proteins called IFNs [33–35].

Orthopoxviruses, such as VACV and Mpox, have developed specific mechanisms to modulate host immune responses. For example, VACV can activate BCL-2-like proteins that prevent the activation of IRF3 and NF-κB, thus allowing the virus to evade the host's innate immune response. Mpox viruses have orthologs of these BCL-2-like proteins, namely A47, B13, P1, C6, and D11. Additionally, VACV produces an E3 protein that binds to double-stranded RNA and prevents its recognition by host PRRs. This inhibits the activation of the protein kinase R (PKR) pathway, which is involved in inhibiting viral replication. Mpox has a similar protein called F3, although it has a truncation at the amino terminus [8, 36].

While the recombinant VACV lacking the ability to suppress innate immune responses does not express Mpox F3L (VACV-F3L) and does not inhibit PKR, Mpox viruses still possess the ability to suppress innate immune responses. This suggests the presence of unidentified proteins in Mpox that compensate for the lack of sufficient F3 protein. Mpox viruses limit the immune activities of the host by employing these mechanisms [37]. Another important transcription factor involved in innate immune responses is IRF3, which stimulates the production of antiviral molecules such as IFN-α and IFN-β. Mpox viruses produce a protein called B19, which directly interacts with IFNs and prevents their binding to receptors. Deletion of the *B19R* gene in Mpox virus significantly reduces infection, indicating that the B19 protein or its ortholog in Mpox likely interferes with IFNβ signaling [38].

In terms of NF-κB activation, orthopoxviruses utilize ankyrin-like proteins to prevent its activation. Mpox viruses encode several ankyrin-like genes, including *B17R*, *D9L*, *J1R*, and *N4R*, as well as other genes such as *J3L*, *D1L*, *D7L*, *O1L*, *C1L*, and *B5R*. These proteins play a role in preventing NF-κB activation, thereby modulating immune responses [33, 34].

TLRs and NOD-Like Receptor Signaling Pathways

TLRs are a family of cell membrane-associated receptors that play a crucial role in the initiation of innate immune responses against pathogens. These receptors are equipped with structural features, such as leucine-rich repeats and the Toll/IL-1 receptor (TIR) domain, which enable them to recognize and respond to specific pathogen-associated molecular patterns (PAMPs) [39–41]. The leucine-rich repeats region of TLRs is responsible for recognizing and binding to various PAMPs, including lipopolysaccharides, proteins, flagellin, RNA, and DNA, which are derived from bacteria, viruses, and fungi. Different TLR members have specialized ligand recognition capabilities; for instance, TLR4 is the main receptor for lipopolysaccharide from Gram-negative bacteria, while TLR3, TLR7, TLR8, and TLR9 are involved in the recognition of viral nucleic acids [42, 43]. Several TLRs have been implicated in the immune response against Mpox infections. The activation of TLR3 in the lungs can increase inflammatory responses and help fight viral replication. TLR9 plays a critical role in the activation of CD11 cells and DCs, which leads to the expression of pro-inflammatory genes, such as IL-6, TNF-α, IL-1β, and IL-12 [44, 45]. This inflammatory response is believed to be essential for combating Mpox-induced infections. Additionally, TLR9 in DCs is crucial for recognizing the Mpox and inducing the recruitment of NK cells to the infection sites [46]. The activation of TLR2 following Mpox infection is also involved in the stimulation and differentiation of memory cells into CD8+ T cells, as well as the activation of NK cells, which leads to the increased production of the antimicrobial peptide cathelicidin (LL-37) in mast cells. However, the specific mechanisms by which Mpox modulates and manipulates the TLR signaling pathway require further research [47].

In addition to the TLR signaling pathway, the NOD-like receptor (NLR) signaling pathway is another important component of innate immune [48]. The NLR members Nod1 and Nod2 recognize specific bacterial and viral components, such as γ-D-glutamyl-meso-diaminopimelic acid (iE-DAP) and muramyl dipeptide, respectively. Upon ligand recognition, Nod1 and Nod2 form oligomers and interact with the receptor-interacting-serine/threonine-protein kinase 2 (RIP2) protein, which activates the MAPK and NF-κB pathways [49–51].

Nod1 and Nod2 are also involved in the induction of autophagy, an innate immune-related process that helps eliminate invading viruses. When Mpox infects the host cells, Nod1 and Nod2 can interact with Atg16L, Atg5, and Atg7 to induce autophagy independently of the RIP2 and NF-κB pathways, thereby regulating antiviral immunity [52–54]. The newly identified sensor AIM2 and caspase-1 play a crucial role in regulating the maturation of interleukin-1 beta (IL-1b) and IL-18 in response to interaction with Mpox viruses. These defense mechanisms help the body mount a more effective resistance against Mpox virus infections. The AIM2 receptor, which detects cytoplasmic viral DNA, interacts with caspase-1 to activate this process, highlighting the importance of this pathway in initiating an effective immune response against poxvirus infections [19, 55].

Inflammasome Activation Pathway

Inflammasomes are complex collections of proteins that have a direct effect on the regulation of IL-1b and IL-18 production, as well as the initiation of the pyroptosis process. This process is considered a planned death. These types of proteins start their activity in response to various infections. With the formation of these large protein complexes, inflammasomes act as a platform for activation of inflammatory signaling pathways that lead to the release of pro-inflammatory cytokines and induction of pyroptosis, which helps kill infected cells and control the spread of pathogens. The key components of an inflammasome are central NLR or absent in melanoma-like receptors 2 (ALR) proteins. In addition, apoptotic adapter protein associated with apoptosis-associated speck-like protein containing a CARD (ASC) and caspase-1 are also considered as the main components of inflammasomes. Activation of any type of inflammasome is mediated by two different signals, including induction of transcription of pro-IL-1b and NLRs or ALRs, and specific NLR/ALRs oligomerization leading to assembly of the inflammasome (Fig. 2) [56–58].

Studies conducted on NLRP3 and AIM2 have shown that their activation causes polymerization of ASC adapter protein. This process is associated with caspase-1 activation. NLRP1 is a complex that is associated with caspase-1 activation. This complex has a CARD that interacts strongly with the CARD domain of procaspase-1. While muramyl dipeptide has been shown to activate the NLRP1 inflammasome; however, the activator of human NLRP1 is still not fully understood, and the activation of this pathway has not been observed following Mpox infection [59, 60].

Mpox infection alters inflammatory signaling, activates caspase-1, and leads to the release of IL-1β, IL-18, and pyroptosis. Inhibitors targeting Mpox infection can affect this signaling. These inhibitors include AIM2, IL-1β, IL-18, ALR, ASC, ROS, SPI-2, TLRs, TRAF6, PYD, HIN-200, and CARD [61]. These strategies allow the virus to suppress the innate immune of the host and persist within the host's cells. One of these strategies involves disrupting the signaling pathways of inflammasomes, which are multiprotein complexes that activate inflammatory responses. Mpox viruses produce proteins that can either prevent the assembly or activation of inflammasomes, thereby inhibiting the secretion of pro-inflammatory cytokines and the initiation of immune responses [62].

Another strategy employed by Mpox viruses is to target and inhibit the function of NLRs and ALRs, which are innate immune sensors that recognize PAMPs and DAMPs (danger-associated molecular patterns) within the host cell. By impairing the function of these sensors, Mpox viruses can evade detection by the host's immune system and create a favorable environment for their replication [63]. Furthermore, Mpox viruses possess other proteins, such as cytokine binding proteins (vIL-1βBPs, vIL-18BPs) that assist in modulating the host's innate immune defenses, viral replication, and productive infection. These proteins help the virus manipulate the immune response of the host and promote its own survival and proliferation (Fig. 2) [64].

NK Cell Pathway

The mechanisms used to activate NK cells during poxvirus infection remain largely unknown and will vary depending on the type of virus. Receptors acting on NK cells include killer cell-like immunoglobulin receptors and NKp65 in humans. Natural cytotoxic receptors (NCRs), NKRP1A, and Ly49s in mice are also among these [65]. These receptors transmit signals through adapter proteins. Among these proteins, we can mention DAP12 and DAP10, which play an important role in the induction of NK cells. Studies conducted on human NK cells have shown that NCRs have some interactions in the process of lysis of fibroblasts infected with VACV. The most important NCRs that perform such interventions include NKp46, NKp44, and in some cases, NKp30 [66]. However, in these studies, no significant role for NKG2D in activation was observed, and there was no evidence of

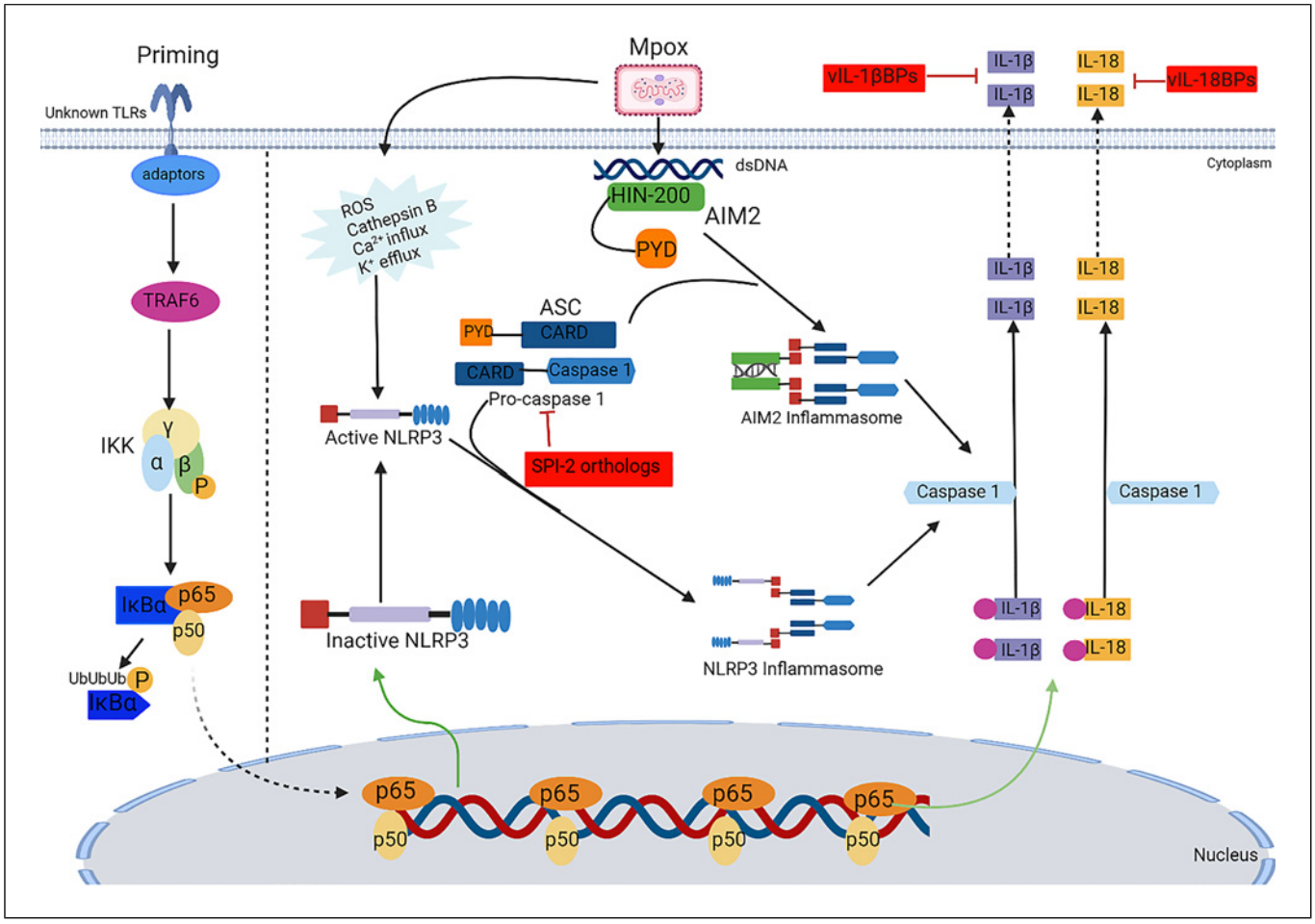

Fig. 2. Modulation of inflammasome signaling by Mpox infection. Inflammasomes are multiprotein complexes that sense cytosolic dsDNA and activate caspase-1, leading to the production of inflammatory cytokines such as IL-1β and IL-18 and the induction of pyroptosis, a form of programmed cell death. The various Mpox inhibitors are shown in red boxes. For more details and the underlying molecular mechanisms, see the main text. AIM2, absent in melanoma 2; IL-1b, interleukin-1 beta; IL-18, interleukin-18; ALR, absent in melanoma-like receptors 2; ASC, apoptosis-associated speck-like protein containing a CARD; ROS, reactive oxygen species; SPI-2, serine proteinase inhibitor 2; TLRs, Toll-like receptors; TRAF6, tumor necrosis factor receptor-associated factor 6; PYD, pyrin domain; HIN-200, hematopoietic IFN-inducible nuclear proteins with a 200 amino acid repeat; ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase activating and recruiting domains.

up-regulation of NKG2D ligands as a result of infection. Recent research has shown that hemagglutinin protein from VACV can interact with NCRs NKp30 and NKp46 in humans [67]. The noteworthy point is that in VACV, by removing the proteins that have viral hemagglutinin properties, lysis of infected cells was seen more. This indicates the existence of an interaction between hemagglutinin and NCRs, which probably prevents the activation and stimulation of NK cells [68]. The hemagglutinin interaction appears to limit NKp30 signaling while reducing NKp46 signaling [69]. However, these findings were based on experiments using chimeric receptors, and it is unclear which ligands are involved in the stimulation of NCRs in the context of poxvirus infection and whether the lineage of the infected cell influences the ligands that trigger NK cell activation [66].

Research has shown that direct TLR2 signaling is important and necessary to stimulate NK cells during Mpox infection [70]. In the activation and function of NK cells, Mpox viruses can directly interact with TLR2 on NK cells, leading to their activation and subsequent immune response [31]. In addition, the NKG2D receptor is involved in NK cell resistance to Mpox disease [71].

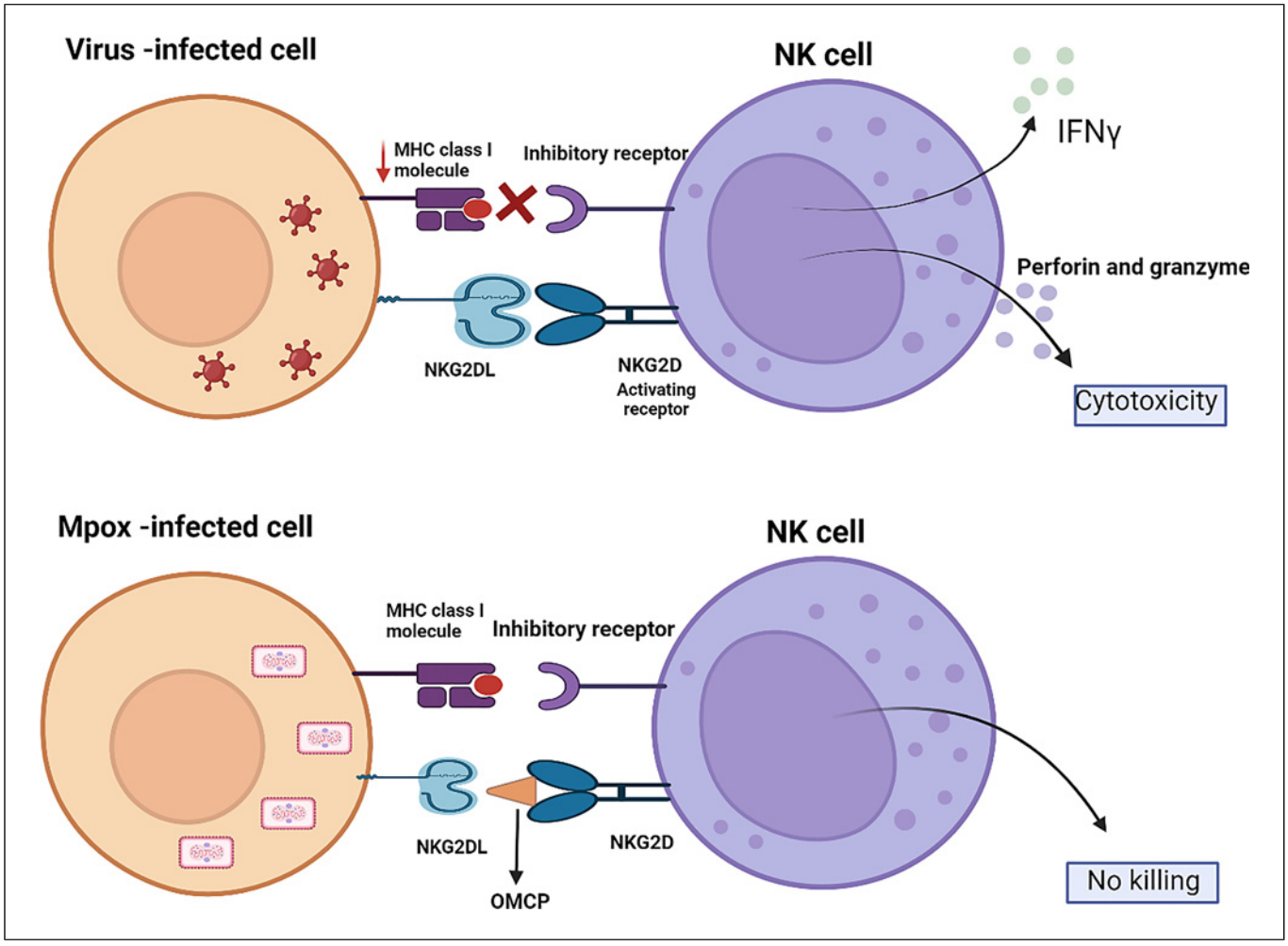

Fig. 3. Modulation of NK cell activation by Mpox infection. NK cells recognize virus-infected cells through the NKG2D receptor, which binds to NKG2D ligands (NKG2DL) that are upregulated by cellular stress and viral infection. NKG2D activation also depends on the downregulation of MHC class I expression on infected cells, which reduces the inhibitory signals from MHC class I receptors. Mpox encodes a secreted MHC class I-like protein (OMCP) that competes with NKG2DL for binding to NKG2D and inhibits NK cell killing.

NKG2D is known as a receptor whose expression is regulated by NK cells that recognize stress-induced ligands on infected cells. It has been shown to be involved in NK cell-mediated killing of target cells during Mpox infection [72]. Activation of the NKG2D signaling pathway in NK cells contributes to their ability to recognize and eliminate Mpox-infected cells (Fig. 3) [66].

Mpox and other orthopoxviruses have developed strategies to evade the immune response mediated by T and NK cells, which are important components in fighting viral infections. T cells identify and eliminate virus-infected cells by recognizing foreign peptides presented on the cell surface through MHC class I molecules [73]. During viral infection, MHC class I molecules can present viral peptides and trigger an immune response. NK cells, on the other hand, detect infected cells by scanning for missing or altered MHC class I molecules, which can indicate viral infection. They use a receptor called NKG2D to recognize stress-induced ligands expressed on infected cells. Mpox produces a protein called orthopoxvirus MHC class I-like protein (OMCP) that can bind to the NKG2D receptor on NK cells, thus evading the NK response. This protein also downregulates MHC class I expression, which helps the virus evade T cell recognition. By weakening the responses of NK and T cells, Mpox can establish a successful infection and avoid immune clearance (Fig. 3) [74].

Apoptosis Pathway

Apoptosis involves the process of programmed cell death, following which virus-infected cells die [75]. Orthopoxviruses can increase their survival and reproduction in the host by interfering with apoptosis [8, 76]. One of the ways that these viruses regulate apoptosis is by producing BCL-2-like proteins that interfere with the intrinsic apoptosis pathway [30]. BCL-2 family proteins can interfere in the regulation of the apoptosis pathway and cause its inhibition [77]. BCL-2-like proteins encoded by orthopoxvirus can limit BCL-2 cellular proteins with pro-apoptotic functions and thus prevent the initiation of apoptosis in infected cells [78]. In addition, orthopoxviruses produce serine protease inhibitors (SPIs), also known as serpins, which interfere with apoptotic pathways. One such inhibitor is cytokine response modifier A (CrmA) encoded by cowpox virus (CPXV) [79]. CrmA is a potent inhibitor of apoptosis and can block the activity of caspase-1, caspase 8, and granzyme B [80, 81]. Granzyme B is known as a protease, its activation is through cytotoxic T cells, and its action induces cell death in virus-infected cells. By inhibiting granzyme B and caspase-1 and 8, CrmA interferes with both apoptotic and pyroptotic pathways, which are important mechanisms for killing virus-infected cells [29]. In VACV, the CrmA homolog is SPI-2. SPI-2 can inhibit apoptosis and in this case it is considered one of the strongest inhibitors [80]. Similar to CrmA, SPI-2 can inhibit granzyme B, caspase-1 and caspase-8, thereby blocking apoptotic and pyroptotic pathways [82]. Mpox encodes an ortholog of SPI-2 through the *B12R* gene. This SPI-2 protein in Mpox probably has similar functions to CrmA and SPI-2 in CPXV and VACV by inhibiting granzyme B, caspase-1, and caspase-8 to escape from apoptosis (Fig. 2) [76, 80].

Tumor necrosis factor receptor (TNFR) orthologs have important functions to prevent inflammasome and apoptosis-related processes [8]. These viral TNFRs act as decoys because they lack signaling domains and are secreted to compete for tumor necrosis factor binding (TNF) [83]. Among orthopoxvirus TNFRs, there are five, and CrmB and CrmC are known as the most important TNFRs. In addition, there are other TNFRs such as CrmD, vCD30, and CrmE [8, 84]. The Mpox genome encodes only one type of these TNFRs, and that is CrmB [30]. Studies on CPXV have shown that CrmB has a high affinity for TNF [85]. These data demonstrate the ability of orthopoxviruses, including Mpox to manipulate host immune responses through the production of viral TNFR orthologs. These viruses can interfere with inflammatory and apoptotic processes by secreting decoy receptors that compete with cellular TNFRs for binding to TNF, potentially aiding their survival and replication in the host (Fig. 1) [86, 87].

Complement System Pathway

Orthopoxviruses adopt various methods to prevent the effect of innate immune responses and in this way, they can suppress them. These viruses secrete proteins that disrupt the pathways of the innate immune system. For example, by disrupting the IFN gamma (IFN-γ) pathway, CC and CXC chemokines, IL-1β, and the complement system [88, 89]. The complement system is an important part of the innate immune response, consisting of a group of proteins that work together to recognize and eliminate pathogens. Orthopoxviruses have the ability to modulate and suppress the complement system. Among the various known Mpox clades, no complement system suppressor proteins have yet been identified in the case of the West African clade. The Central African clades encode a protein known as Mpox inhibitor of complement enzyme (MOPICE). This protein is encoded by the *D14L* gene [90–92]. MOPICE plays an important role in preventing complement activation. This protein does this by binding to C3 and C5 convertases, which are key enzymes involved in the complement cascade [93, 94]. However, studies have shown that deletion of MOPICE from Central African Mpox strains does not significantly affect virus virulence in rhesus monkeys infected with Central African isolates [95]. Although MOPICE does not appear to be essential for Mpox virulence, its absence reduced the adaptive immune response in infected animals. This suggests that although MOPICE may not play a role in virulence, it modulates adaptive immunity in the host [12].

Innate Immunity Challenges in Immunocompromised Patients Facing Mpox

Immunocompromised individuals, including those with human immunodeficiency virus (HIV), cancer, organ transplants, or on immunosuppressive drugs, face a heightened risk of severe Mpox symptoms. These can manifest as widespread rashes, potentially leading to secondary bacterial or fungal infections, tissue death, and obstructions in the digestive system. Additionally, they may suffer from complications in the heart, lungs, urinary tract, and nervous system, with symptoms like maculopapular rashes and pustules across various body parts, and lymphomas in the head and neck area. The most severe outcomes for these patients can include respiratory

failure, renal impairment, and systemic organ failure [96–98].

In cancer patients, triggering the innate immune response has been proposed as a novel immunotherapeutic strategy to counteract tumor-induced immunosuppression [99]. This approach aims to activate innate immune cells, particularly NK cells and macrophages, which are less suppressed compared to adaptive immune cells in certain cancer patients [100]. By enhancing the innate immune response, there is a potential to improve therapeutic outcomes in cancer patients. Moreover, in sepsis-induced immunosuppression, which shares similarities with the immunosuppression seen in Mpox and cancer, there is a complex interaction between innate and adaptive immunity. Sepsis leads to cellular dysfunctions that result in immunosuppression affecting both arms of the immune system. The dysregulation of immune responses in sepsis highlights the importance of understanding and potentially modulating the innate immune response in conditions where immunosuppression is a concern [101].

Conclusion

Mpox is a reemerging viral disease that poses a global threat in the aftermath of COVID-19. The origin and transmission of this virus are still unclear and it can evade or manipulate the host immune system in various ways. This article reviewed the role of innate immune pathways, such as TLRs, NLRS, inflammasome, and NKG2D. In detecting and defending against Mpox infection, as well as the strategies that Mpox uses to counteract these pathways, such as encoding SPI-2, MOPICE, OMCP, and BCL-2 – like proteins. These mechanisms enable Mpox to persist and spread in the host cells, causing different signs and symptoms. Further research is needed to uncover more aspects of the interaction between Mpox and the innate immune system, and to develop effective treatments and prevention measures for this discuss. Furthermore, understanding the innate immune response to Mpox in immunosuppressed patients is crucial for the development of effective therapeutic strategies. By exploiting the capabilities of the innate immune system and considering the interplay between innate and adaptive immunity, novel approaches to the management of Mpox and other conditions characterized by immunosuppression can be explored.

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Reza Parnian and Fatemeh Heydarifard wrote the first draft of the manuscript. Fatemeh Sadat Mousavi, Zahra Heydarifard, and Milad Zandi edited the manuscript. Zahra Heydarifard designed the figures. Milad Zandi supervised the study. All authors reviewed and approved the final version of the manuscript.

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