APJAI
Asian Pacific Journal of
Allergy and Immunology

REVIEW ARTICLE

Mpox global health emergency: Insights into the virus, immune responses, and advancements in vaccines

PART I: Insights into the virus and immune responses

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Abstract

Mpox, the zoonotic disease caused by Monkeypox virus (MPXV), is currently a global health emergency. This review (Part I) aims to provide insights into the virus life cycle, epidemiology, host immune responses, and immune evasion mechanisms. Mpox symptoms is similar to smallpox but with lower mortality rates and lower transmissibility. In the past, the virus has been endemic in Central (Clade I) and West (Clade II) African countries. The first outbreak in outside Africa is reported in the United States in 2003. A multi-country outbreak across all continents occurred in 2022, predominantly driven by Clade II. Recently, the emergence of Clade Ib with sustained person-to-person transmission characteristic in the 2023-2024 outbreaks has raised significant public health concerns. Its apparent capacity for rapid spread and potential for causing severe disease highlight the need for enhanced surveillance, especially in regions not traditionally affected by Mpox. Immune responses induced by MPXV infection in humans and animal models provide the insights into the key step in which the host immune response recognizes and responds to the infection. The sophisticated immune evasion strategy by MPXV at both innate and adaptive arms also emerges that are useful for vaccine-based control measures. Taken together, understanding MPXV life cycle, epidemiology and immune response will facilitate better control, limit viral spread, and provide important insights for vaccine development.

Key words: Monkeypox virus, Mpox, MPXV, Epidemiology, Viral Life Cycle, Immune Response

Citation:
Prompetchara, E., Ketloy, C., Khawsang, C., Ruxrungtham, K., Palaga, T. (2024). Mpox global health emergency: Insights into the virus, immune responses, and advancements in vaccines PART I: Insights into the virus and immune responses. *Asian Pac J Allergy Immunol*, 42(3), 181-190. https://doi.org/10.12932/ap-111024-1945

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Introduction

Monkeypox Virus (MPXV) was first identified in monkeys in 1958 and the transmission to humans was later identified. The following up studied revealed that various mammals, including rodents and non-human primates are susceptible to MPXV infection. In the past, sporadic outbreaks in human were reported, but mostly limited to Central and West Africa. In 2003, the first outbreak in the US that included 47 confirmed cases were caused by the imported animals from Africa. In 2022, however, a major global outbreak was found with cases reported in non-endemic countries, including Europe, North America, and Australia. These series of outbreak led the WHO to declare Mpox as a Public Health Emergency of International Concern (PHEIC) in July 2022. This review integrates novel insights into the biology of MPXV, immune responses upon infection and immune evaion, and the latest developments in vaccines.

Nature and origin of the Mpox virus (MPXV)

Mpox, formerly known as monkeypox, is a zoonotic disease caused by the monkeypox virus (MPXV).[1] It is a member of the *Orthopoxvirus* genus within the *Poxviridae* family. This genus also includes other notable viruses such as variola virus (causative agent of smallpox), cowpox virus, and vaccinia virus (used in smallpox vaccines).[2] MPXV was initially identified in 1958 in laboratory monkeys colony in Denmark. It is known for causing symptoms similar to smallpox but with lower mortality rates.[3] The first human case was reported in a 9-month old child admitted for suspected smallpox in 1970 in the Democratic Republic of Congo.[4] Its primary reservoirs believed to be rodents and other small mammals, including squirrels, dormice, and Gambian pouched rats.[5] The natural origin of the virus is thought to be in forested regions of Central and West Africa, where it is transmitted to humans through direct contact with the infected animals body fluids or through bites or scratches.[6] Human-to-human transmission occurs through respiratory droplets during prolonged face-to-face contact, direct contact with body fluids, or exposure to virus-contaminated objects.[7] Although MPXV is less contagious (reproduction number, R0 around 1.46-2.67)[8] than smallpox (smallpox R0 = 3.5 to 6),[8,9] the recent global outbreaks have been raised concerns about its potential for widespread transmission and its public health implications especially in the context of healthcare settings as well as in the MSM community.[10,11] The first global outbreak occurred in mid-2022, leading the World Health Organization (WHO) to declare the outbreak a PHEIC on July 23, 2022.[12] Over the past two years, despite a decrease of the overall Mpox cases, they have continued to be reported globally. In mid-2024, the incidence of Mpox cases gradually increased with a new dominant clade (clade Ib replacing clade II). Consequencely, WHO declared a the current outbreak caused by clade Ib as a PHEIC on August 14, 2024.[13]

Genomes and replication

The MPXV has a large, double-stranded DNA genome of approximately 197 kilobases (kb), encoding more than 200 proteins. The genome is flanked by inverted terminal repeats (ITRs) that play a role in their replication and stability. The coding region contains several genes that are homologous to other orthopoxviruses, but its unique genes that may contribute to its unique pathogenic profile. The genome of the MPXV is organized into central, conserved regions responsible for essential viral functions (such as replication, transcription, and assembly) and variable terminal regions that contain genes involved in host immune evasion, virulence, and host range.[14,15] (**Figure 1**)

Unlike most DNA viruses that replicate in the host nucleus, MPXV replicate entirely within the cytoplasm of infected cells. The MPXV replication cycle consists of several stages including viral entry, uncoating, early transcription, DNA replication, late transcription, assembly, and release.[16] In detail, the MPXV virion initially attaches to the host cell membrane through interactions between viral surface proteins and host cell receptors, comprehensively described elswhere.[17] While the exact receptors for MPXV are not fully characterized, studies have suggested that glycosaminoglycans (GAGs) on the cell surface play a role in facilitating viral entry.[18] After binding, MPXV can enter the cell by two potential mechanisms. The first mechanism is membrane fusion in which the viral envelope fuses directly with the host cell membrane, releasing the viral core into the cytoplasm. Alternatively, the virus may be internalized via endocytosis, followed by fusion with the endosomal membrane to release the viral core.[19] Once inside the cytoplasm, the viral envelope is removed, exposing the viral core. Early genes expression involves the expression of early genes, which are transcribed by the viral DNA-dependent RNA polymerase packaged within the viral core. Early genes primarily encode enzymes and factors necessary for viral DNA replication and immune evasion. These processes occur in the viral factories formed within the cytoplasm. After early gene expression, the viral DNA replication machinery assembles in the cytoplasm. The replication process begins with the formation of a replication complex in the cytoplasm. After DNA replication, late genes are transcribed and translated. These genes encode structural proteins, enzymes required for the assembly and maturation of new virions, and proteins involved in host cell exit. Structural proteins produced in the late phase begin to form immature viral particles. These particles serve as precursors for mature virions and consist of a lipid membrane, viral DNA, and associated proteins. Immature virions are initially formed as spherical particles containing the viral genome and core proteins. The immature virions undergo a series of conformational changes and proteolytic cleavage of core proteins to become mature virions (MVs). This process involves the condensation of the core, rearrangement of the viral membrane, and formation of lateral bodies. Some mature virions acquire an additional membrane from the golgi apparatus or endosomes, forming intracellular enveloped virions (IEVs). These enveloped forms are involved in cell-to-cell spread. There are two pathways of virions release, Firstly, IEVs are transported to the cell surface along microtubules and are released from the cell by exocytosis as extracellular enveloped virions (EEVs). EEVs are thought to be important for long-range dissemination of the virus within the host. Secondly, non-envelopped intracellular mature virions (IMVs) can also be released through cell lysis, leading to the death of the host cell. IMVs are thought to be more stable in the environment and are likely involved in transmission between hosts (**Figure 1**).

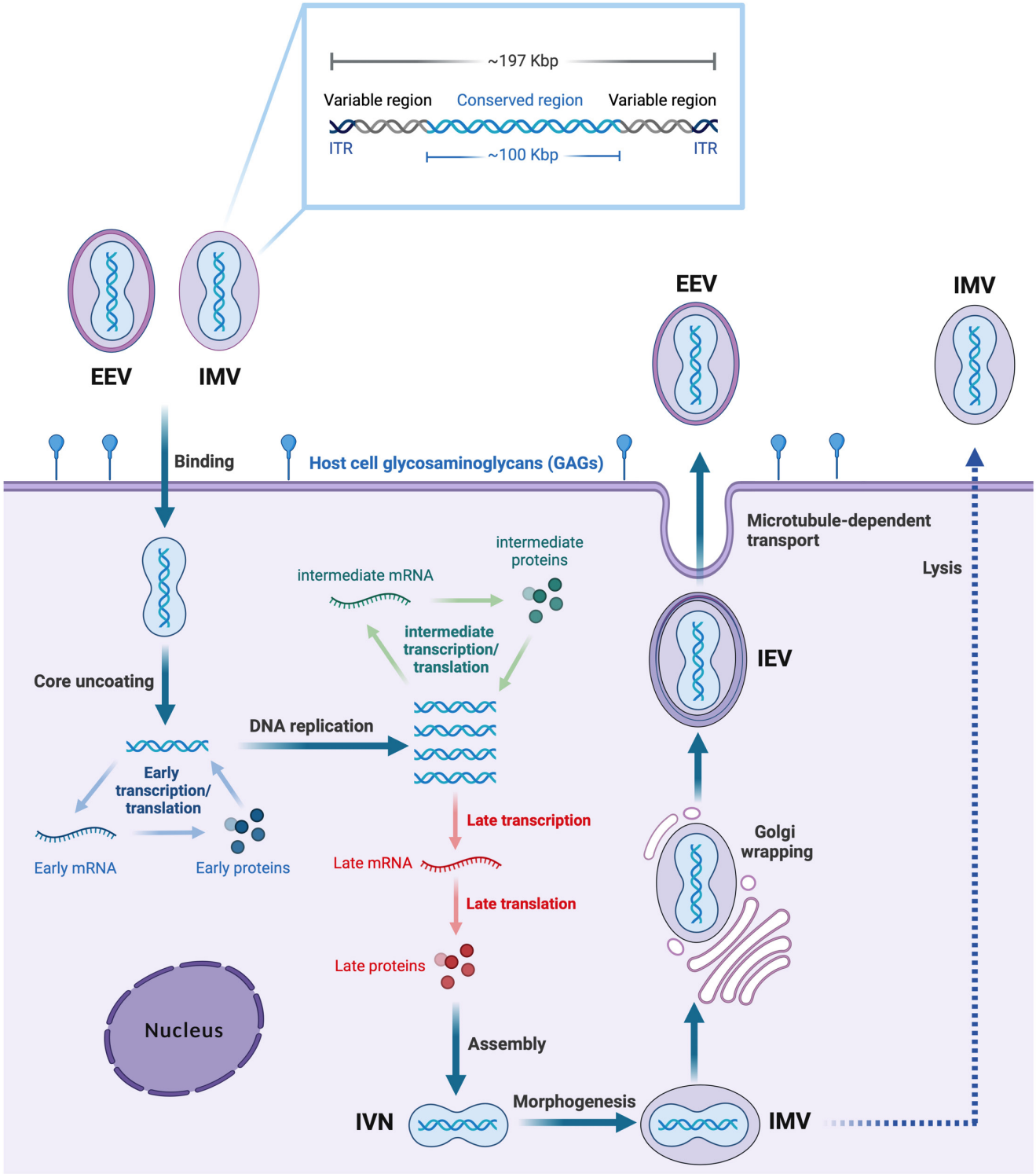

Figure 1. The schematic representation of MPXV life cycle. Both infectious forms of MPXV-extracellular enveloped virion (EEV) and intracellular mature virion (IMV) use their surface proteins to attache to host cell receptors, including glycosaminoglycans (GAGs). After the virion binds and fuses with the host cell membrane, the viral core is released ino the cytoplasm, initiating early transcription using the DNA-dependent RNA polymerase carried within the viral core. Viral DNA replication occurs in the cytoplasm, followed by late transcription and translation to produce stuctural proteins and enzymes required for the assembly and maturation. Viral assenbly takes place by wraping the viral gemome to form immature virions with nucleoli (IVN). The IVNs then mature into intracellular mature virions (IMVs). Some IMVs accuire an additional envelope from the Golgi apparatus, forming an intracellular enveloped viruses (IEVs). IEVs use microtubules in Golgi apparatus to move to the cell surface, where they are released as extracellular enveloped virions (EEVs). Alternatively, IMVs can also be released through cell lysis, leading to the death. (*Created with Biorender*)

Epidemiology

This rapid review aimed to evaluate and quantify the rePrimarily, the disease is endemic in parts of Central and West Africa, where it is transmitted from animals to humans. In recent years, cases have also been reported outside Africa, highlighting its potential as an emerging global health threat. The first human Mpox case outside Africa was detected in 2003 in the United States, marking the first outbreak of Mpox in the Western Hemisphere.[20] This outbreak resulted in 47 confirmed and probable cases across six states in the US. There were no deaths, but the outbreak highlighted the potential for Mpox to spread in non-endemic regions.[21] Mpox epidemiology is marked by sporadic outbreaks, both in endemic regions and globally. In details, the early endemic outbreaks in Africa during 1970s to early 2000s, involved Clade I in the central Africa (or Congo Basin) and Clade II in West Africa. MPXV clades nomenclature used in this review is in line with the suggestion of Happi et al.[22] Most cases were zoonotic, with limited human-to-human transmission.[23] The outbreak in the USA in 2003 and re-emergence in Nigeria during 2017-2019 was Clade II.[20,24] In 2022, multi-country outbreak with thousands of cases reported across Europe, the Americas, and Asia was also predominated by Clade II. New sub-clades (IIa and IIb) were introduced to represent the genetic diversity seen in this outbreak.[25] Unlike previous outbreaks, the 2022 outbreak demonstrated sustained human-to-human transmission, particularly among social and sexual networks, which was unprecedented for Clade II strains.[26] The enhanced human-to-human transmission was hypothesized to be driven by an apolipoprotein B messenger RNA editing enzyme, catalytic subunit 3 (APOBEC3) cytosine deamination, which accelerates viral evolution.[27,28] Remarkably, Clade Ib has emerged as a notable variant in the 2023-2024 outbreaks.[12] It was identified through genomic sequencing efforts in eastern region of Democratic Republic of the Congo Mpox outbreaks in late 2023 and in early 2024.[29] It is relatively higher transmissibility and pathogenic potential.[30] Recently, infections have been identified in additional African countries that had previously not reported any Mpox cases caused by clade Ib virus. Notably, three clade Ib imported cases were confirmed in Sweden on 15 August 2024, in Thailand on 22 August 2024, and in India on 23 September 2024.[31] The emergence of Clade Ib has significant implications for public health. Its apparent capacity for rapid spread and potential for causing severe disease necessitates enhanced surveillance, especially in regions not traditionally affected by Mpox. Since 1 January 2022, according the recent report from the WHO,[32] the laboratory-confirmed cases of Mpox have been reported from 123 countries across all continents, **Figure 2**. As of 31 August 2024, a total of 106,310 laboratory-confirmed cases with 234 deaths have been reported. Interestingly, number of suspected case remains high (more than 35,000 cases since January 2024) in Africa. Among these suspected cases, approximately 50% were later confirmed.

Similarities and differences between MPXV and Smallpox viruses

Compare to smallpox, Mpox has several differences and similarities in terms of their virology, epidemiology, clinical manifestations, and management, **Table 1**.

Table 1. Comparison of Smallpox and Mpox viruses.

Feature	Mpox	Smallpox	Comments
Causative Agent	Monkeypox virus (MPXV)	Variola virus	Both are Orthopoxviruses
Clades	Two main clades: Clade I (Congo Basin) and Clade II (West African)	None	- Two sub-clades of clade II were identified during 2022 multi-countries outbreak - New sub-clade of clade I (Ib) has emerged during 2024 oubreak - Clade I has a higher case fatality rate (CFR) compared to Clade II.
Natural Reservoir	Rodents (e.g., squirrels, rats) and possibly primates	Humans	Smallpox has no animal reservoir; Mpox is a zoonotic disease with animal reservoirs.
Transmission	Zoonotic transmission via contact with infected animals or human-to-human transmission similar to smallpox	Human-to-human via respiratory droplets, direct contact with bodily fluids, or contaminated objects	Sexually transmitted infection has been confirmed for Mpox
Contagiousness	Less contagious Reproduction number (R_0) = 1.46-2.67[8]	R_0 = 3.5 to 6[8,9]	
Vaccine	- No specific Mpox vaccine approved, but under development - Smallpox vaccines agiants provided partial protection against Mpox	Vaccinia virus vaccine is partially effective against smallpox (see Table 3)	- Several vaccine cadidated against Mpox are being developed - Three smallpox vaccines emergency approved for Mpox (country-specific approved)

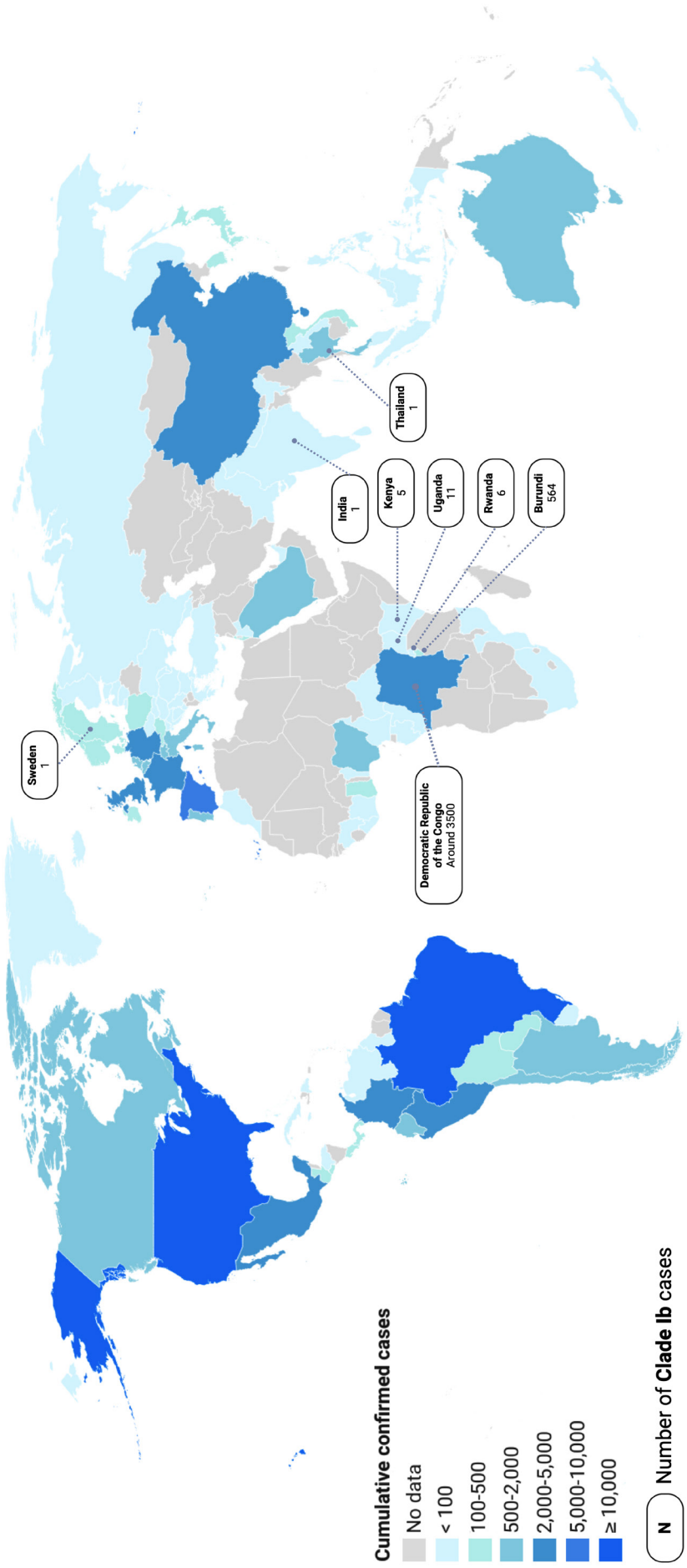

Figure 2. The epidemiology of Mpox, showing cumulative confirmed cases in each country since January 2022 to 4 September 2024 (data from www.ourworldindata.org (Mpox: Cumulative confirmed and suspected cases).[33] The presence of clade Ib and number of Mpox cases caused by clade Ib during the 2022-2024 outbreak is show (Data were from World Health Organization, Mpox Multi-country external situation report no.39, published 6 October 2024.[32]

Understanding the life cycle and epidemiology of MPXV, as well as its characteristics compared to another important orthopoxvirus, Variola virus, is becoming increasingly important to understand how the host immune system responds to MPXV. MPXV shares various characteristics with other orthopoxvirus, including immunodominant antigens and the mechanisms of immune evasion. Analyzing and comparing the immune response to MPXV and variola virus and vaccinia virus is essential for exploring how the human immune system reacts to MPXV infection and the factors that influence the immune protection. Moreover, it could help mitigating disease severity and provide valuable information for developing effective vaccines and therapeutic strategies.

Immune response to MPXV infection and immune evasion

Immune Profiles of MPXV-infected Individuals

The study of the immune response in individuals during the Mpox outbreak in 2003 and the characterization of vaccine responses provided crucial information regarding the host-MPXV interaction. In an *in vitro* restimulation assay, PBMCs from MPXV or vaccinia virus-immunized individuals were exposed to MPXV or vaccinia virus infection and the response was evaluated by intracellular cytokine staining for IFNγ and TNFα. Interestingly, $CD4^+$ and $CD8^+$ T cells from these individuals did not respond to MPXV-infected cells, in contrast to the robust response against vaccinia virus-infected cells. The mechanism of suppressing T cell activation by MPXV is via an *in trans* mechanism that is not due to downregulation of MHC molecules.[34] In a prospective immunological survey of the 2003 outbreak, data showed a significant drop in Orthopoxvirus-specific IgM levels one year post-infection, while IgG, CD4+, and CD8+ T cell levels remained relatively stable.[35] Interestingly, the immune response levels were not significantly different between individuals vaccinated against smallpox and non-vaccinees. In another study, the humoral immune responses of JYNNEOS, a vaccine approved for Mpox,[36] recipients were compared to those of MPXV-infected patients. The second dose of the vaccine raised.IgG titers to levels comparable to those seen in MPXV infection. Furthermore, vaccinia virus vaccine recipients exhibited long-lasting cellular responses against MPXV.[37]

Immune responses induced by MPXV infection (all mild cases without medical intervention) were compared to those induced by vaccination with JYNNEOS. Two doses of the vaccine induced MPXV-specific IgG responses, with varying degrees among the samples (A29L, E8L, A30L, and A35R); however, only minimal specific responses were detected against the viral cell lysate. In contrast, convalescent serum showed robust responses to all of the aforementioned antigens, including the viral cell lysate. Neither the number of circulating plasmablasts nor the diversity of the V domain of the heavy chains increased with either one or two doses of the vaccine. In contrast to the humoral response, vaccination induced robust, specific $CD4^+$ and $CD8^+$ T cell responses, as measured by activation-induced markers and intracellular cytokine staining (TNF-α, IFN-γ, IL-4, IL-10, and Granzyme B).[36] Infection induced a higher frequency of specific $CD4^+$ T cells, while similar levels of $CD8^+$ T cells were observed in both the infected and vaccinated groups. Interestingly, circulating follicular helper T cells were significantly more robust following vaccination compared to infection, and mixed Th1/Th2 (multiple cytokine-producing) responses were also observed. This study highlighted key differences in the immune profiles induced by MPXV infection and JYNNEOS vaccination, which may provide insights into the protective immunity required for MPXV infection.

In serum samples collected from MPXV-infected patients in endemic regions of Africa (specifically in the Democratic Republic of the Congo) and analyzed using a 30-plex cytokine panel, all key cytokines and chemokines, including IL-1β, IL-1RA, sIL-2R, IL-4, IL-5, IL-6, and IL-8, were elevated in all samples, regardless of symptoms.[38] In severe cases, significantly lower concentrations of IL-6 and IL-1β were observed. The levels of sIL-2R, IL-10, and GM-CSF correlated with disease severity.[38] The results suggest that in the most severe cases of MPXV infection, dampening of the immune response may be a hallmark of the immune profile, potentially involving regulatory T cells (**Figure 3A**).

Immune Responses in Animal Models

Studies of MPXV infection in laboratory animals have provided valuable immunological insights into the immune response induced by MPXV and potential protective mechanisms. Non-human primates (NHPs) and rodents are commonly used as animal models for orthopoxvirus infections, including MPXV.[39] General inbred mice commonly used in immunological research, such as BALB/c mice, are relatively resistant to MPXV infection. Among a panel of 38 inbred strains, the wild-derived CAST/EiJ mouse strain shows high susceptibility to orthopoxvirus challenges, including MPXV.[40] Characterization of the immune response in CAST mice, compared to other inbred strains, revealed a delayed innate immune response (IFN-γ and TNF-α) and reduced numbers of NK and T cells.[41] This delay resulted in uncontrollable viremia and lethality. However, administering IFN-α, IFN-γ, or IL-15 to expand NK cells rescued this mouse strain's susceptibility, suggesting that early innate immune responses and cellular immunity (NK cells) play pivotal roles in controlling MPXV infection (**Figure 3A**).[42]

In NHP models, both aerosolized and intravenous routes of infection are used to study immune responses following MPXV infection or vaccination. The sequence of the body's response to MPXV infection via the aerosol route in cynomolgus macaques has been documented.[43] The viral genome was detected in the lungs by day 2 and had spread to other tissues by days 4–8. IL-8 levels rose rapidly by day 2, while other cytokines (IFN-γ, IL-6, and MCP-1) increased by day 4. Levels of IFN-γ, IL-1Ra, IL-6, IL-8, and

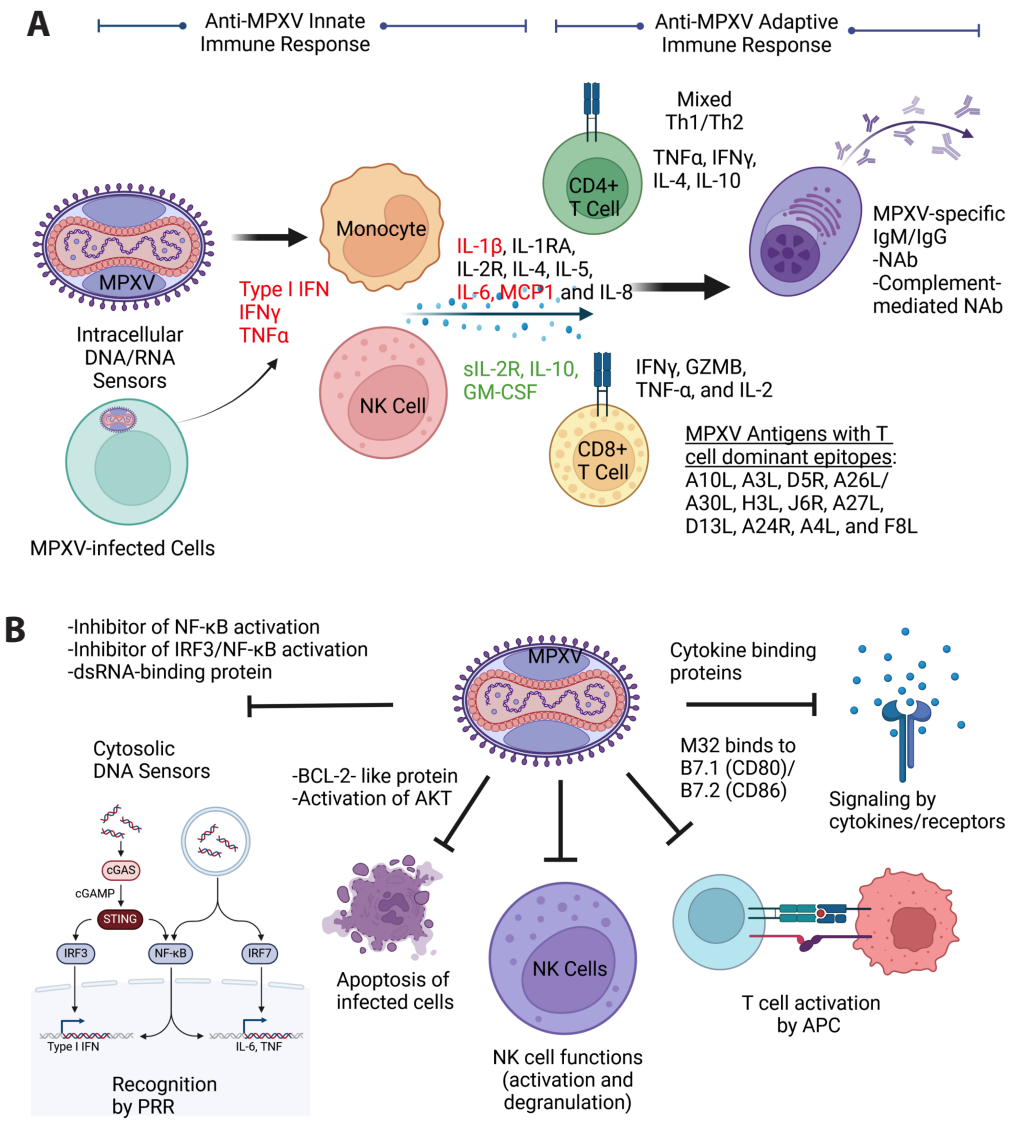

Figure 3. Immune Response Induced upon MPXV Infection and Immune Evasion Strategy of MPXV.
A. Host cells detect infection using intracellular DNA/RNA sensors that trigger an innate immune reaction, including innate cytokine production. Monocytes and NK cells are key players in the innate immune response against MPXV infection. A mixed cytokine profile of Th1 and Th2 responses is observed, while MPXV-specific IgM and IgG are produced with neutralizing activity. The antigens of MPXV that are immunodominant for T cells are highlighted. Cytokines shown in red indicate key cytokines whose levels decreased in severe Mpox, while cytokines shown in green indicate those at higher levels in severe Mpox.
B. MPXV employs multi-pronged strategies to evade the host immune response. During innate immune activation, MPXV evades immune recognition and delays cell death through viral proteins. NK cells become non-functional due to their inability to release granules that kill infected cells. MPXV encodes multiple proteins that can intercept cytokines and receptors to interfere with cytokine functions. The MPXV M32 protein binds to co-stimulatory molecules (B7.1 (CD80) and B7.2 (CD86)) on antigen-presenting cells (APCs), resulting in the suppression of T cell activation. (*Created with Biorender*)

MCP-1 peaked around day 8. By day 10, IgG specific to vaccinia virus proteins became detectable, and by day 12, the animals showed signs of recovery.[43] In an intravenous MPXV infection in rhesus macaques (Macaca mulatta), a robust expansion of NK cells was observed in both the circulation and lymph nodes from days 2 to 8. However, this increase in NK cell numbers did not translate into protection, as MPXV infection impairs NK cell function by inhibiting degranulation and suppressing IFN-γ and TNF-α secretion.[44] Investigating how MPXV suppresses NK cell functions may offer a novel strategy for controlling MPXV infections.

In a serological study involving cynomolgus macaques, MPXV Clade I infection induced a robust IgM response targeting multiple MPXV proteins, with the highest binding observed to intracellular mature virus (IMV) proteins (A44R, F13L, and A33R).[45] These specific IgM antibodies were switched to specific IgG in the recovered monkeys. Sera from smallpox vaccine (Dryvax) recipients also recognized these antigens from MPXV, indicating a substantial cross-reactive humoral response triggered by both MPXV infection and smallpox vaccination.[45]

Immune evasion by MPXV

Orthopoxviruses are equipped with various tools to evade attacks from host immune cells. Their genomes, which encode approximately 200 or more genes, target multiple steps in both the innate and adaptive immune responses. Among the immunomodulatory proteins employed by poxviruses, some are shared among members of the family, while others are unique to MPXV. Furthermore, different clades of MPXV also exhibit variations in their immunomodulatory strategies, which may help explain the differences in virulence among these clades. The general mechanisms of immune evasion used by orthopoxviruses have been extensively reviewed elsewhere[46] and the focus will be placed on the immune evasion strategies utilized by MPXV in this review.

Based on the similarities between MPXV and other orthopoxviruses, the strategies employed by MPXV to achieve immune evasion can presumably be divided into three steps: 1) inhibition of innate immune recognition during the early phase of infection and apoptosis; 2) suppression of the inflammatory response through the production of cytokine mimics or decoy receptors; and 3) suppression of adaptive immune activation (**Figure 3B**).

Upon infection, innate immune cells utilize pattern recognition receptors (PRRs) to detect pathogen-associated molecular patterns (PAMPs). MPXV replicates exclusively in the host cytoplasm and employs multiple mechanisms to recognize cytosolic PAMPs, including cyclic GMP-AMP synthase (cGAS), stimulator of interferon genes (STING), absent in melanoma 2 (AIM2), and interferon gamma-inducible protein 16 (IFI16).[47] Upon PAMP recognition, an antiviral response orchestrated by type I interferons is initiated, which limits viral replication and spread. MPXV encodes several proteins that potentially function to suppress PRR recognition and the activation of downstream type I interferons. These proteins include inhibitors of NF-κB activation/BCL-2-like proteins, inhibitors of IRF3/NF-κB activation, and dsRNA-binding proteins.[48]

In a study comparing Clade I (Congo Basin strain) and Clade II (West African strain) of MPXV, Clade I MPXV was found to increase phosphorylation of AKT, which results in the inhibition of apoptosis. A pharmacological inhibitor of the AKT pathway reduced viral replication.[49] Additionally, the MPXV protein BR203 plays a role in preventing host cell apoptosis.[50]

Cytokines and chemokines play important roles in coordinating host immune responses. The MPXV genome contains various genes that encode proteins capable of interfering with the cytokine and chemokine systems. These proteins include IFNα/β binding proteins, IFNγ binding proteins, TNF and chemokine binding proteins, IL-1β binding proteins, IL-18 binding proteins, and CC chemokine binding proteins.[48] BR-209, encoded by MPXV of Clade I, functions as an IL-1β binding protein and inhibits IL-1β from binding to its receptor. Clade II MPXV contains some mutations in this gene. The inhibition of IL-1β function is expected to dampen the host immune response, thereby impairing the ability to control the virus.[51] Some of these cytokine and chemokine orthologues exhibit robust inhibitory activity against their target cytokines, which may be beneficial for applications aimed at controlling pathological inflammatory conditions. In a comparative transcriptome analysis of cells infected with MPXV, cowpox virus, and vaccinia virus, common gene clusters associated with epidermal growth factor family members and genes involved in the regulation of MAPK activity were identified. Interestingly, MPXV and cowpox virus induced genes related to chemotaxis and leukocyte migration, which were not observed in the attenuated vaccinia virus.[52]

The secreted M2 protein is a member of the poxvirus immune evasion family and is conserved among orthopoxviruses, including variola virus (smallpox), cowpox virus, and vaccinia virus. M2 is classified as an early gene that has been shown to interfere with key signaling pathways in the host immune response, such as ERK and NF-κB, as demonstrated by vaccinia virus M2.[53] Recent studies on the structural properties of the MPXV M2 protein revealed that oligomeric M2 binds to the two surface proteins B7.1 (CD80) and B7.2 (CD86) with high avidity.[54] B7.1 and B7.2 are critical for sending co-stimulatory signals to T cells by binding to CD28 and CTLA-4, resulting in T cell activation. In the presence of M2, T cell activation could not be achieved despite CD3 signaling.[54] Thus, MPXV, similar to other orthopoxviruses, may disrupt key antiviral immune pathways of the cell-mediated immune response by competing with B7.1/B7.2 through M2 binding (**Figure 3B**).

Acknowledgement

We would like to thank the funding support through the Center of Excellence in Vaccine Research and Development (Chula VRC). We are also thankful for the the UK International Science Partnerships Fund (ISPF) Institutional Support Grant (ODA) awarded to the University of Sheffield (Prof. Tuck Seng Wong and Dr. Kang Lan Tee) with Chulalongkorn University (Prof. Kiat Ruxrungtham) as the international project partner. We would also like to acknowledge the assistance of ChatGPT for providing English language editing support in the preparation of this article.

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