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Review

Unveiling Monkeypox virus emergence: What unfolded in the aftermath of the COVID-19 threat?

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ABSTRACT

A new emerging virus named Monkeypox virus (MPXV) has recently gained significant attention, captured the headlines and spread panic among people due to the threat it poses to their health and well-being. This review paper aims to provide an overview of the virology of this novel virus, shedding light on its morphology, genetics, and process of replication. Furthermore, it delves into the origin of the virus and describes the diverse routes through which it spreads, as well as our body's immune response against it. Understanding the fundamental characteristics of the MPXV is crucial in order to comprehend its potential impact on public health. Also, exploring its genetics, and studying its replication would aid in the development of effective diagnostic methods and potential treatments, and to identify specific genes and proteins that contribute to its virulence and pathogenicity. While the likelihood of MPXV becoming a pandemic may be low, comprehensive knowledge about the virus and its modes of transmission is crucial to prevent the possibility of large-scale outbreaks. By staying informed and implementing appropriate preventive measures, we can effectively mitigate the impact of this emerging virus and safeguard public health.

KEYWORDS: Monkeypox virus, emergence, epidemiology, virology, transmission, immunity.

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INTRODUCTION

The human race has survived many epidemics caused by newly emerging and reemerging viruses [1, 2], where a significant increase was noticed by the second half of the 20th century [3]. As is the case of the novel emergent Monkeypox virus (MPXV), a zoonotic pathogenic DNA virus that belongs to the Poxviridae family, that causes an infectious and progressive smallpox-like disease called Monkeypox (Mpox) which became a major public health problem [3-6]. Global cases since the outbreak's beginning reached their highest value in August 2022; then, they gradually decreased and became stable, reaching 84,716 cases as of January 16, 2023. However, the virus's potential for mutation or evolution and the relaxation of safety measures could result in more waves of the outbreak [7]. Upon encountering these reports, we have been compelled to actively engage in efforts to contribute towards disseminating knowledge surrounding Monkeypox virus and awareness about its impact on our health.

Emerging viruses and diseases

Emergence means the appearance of a new phenomenon within a complex system [8], and in the case of viruses it indicates their sudden appearance in human populations through an animal reservoir [9], causing identifiable pathologies and emerging diseases that can develop into pandemics with high mortality rates [3]. These emergent viruses include three virus types: viruses

that have not been previously identified (emerging), viruses that have not occurred as species before, or viruses that have appeared previously but were geographically limited (re-emerging) [10]. Nearly, all emerging viruses have zoonotic origins like coronaviruses implicated in the latest COVID-19 pandemic [11-13], and this viral emergence represents one of the big risks to public health and economy [9, 14]. According to the Institute of Medicine of the National Academy of Sciences in the United States of America (USA), many factors that are grouped in three significant categories contribute to the emergence of new infectious agents and diseases [3].

a. Natural evolution of viruses

Most emerging viruses possess RNA genomes [8, 15], which mutate faster than DNA viruses [16] due to their short generation times [17], resulting in errors made by RNA-dependent RNA polymerase enzymes during replication [3].

b. Changes in human behavioral and social status

Behaviors and habits such as engaging in sexual contacts, and intravenous drug use [17], along with the consumption of raw or undercooked food, contribute greatly in the emergence of viral diseases [18]. Furthermore, the combination of demographic pressures triggering migration to new territories [8] and the substantial increase in international trade and transportation over the past three decades have additionally contributed to the spread of these emergent viruses [19, 20]. Moreover, other factors such as immunity, nutritional state, herd immunity, new medical interventions, low education levels, war and famine also play a significant role [21, 22].

c. Environmental changes

Climate change and global warming modify the geographical distribution of vectors which contribute to virus transmission [8, 23]. Also, rainforest development increases the human-animal contact that leads to the transmission of infectious pathogens from their original hosts to new human hosts [24]; in addition, it is important to acknowledge the role of deforestation in facilitating the emergence and propagation of novel viruses and diseases [3, 17, 25].

Epidemiology of MPXV

Monkeypox virus was isolated for the first time in 1958, after an outbreak of a non-fatal rash disease occurred in a laboratory of monkeys at State's Serum Institutes in Copenhagen, Denmark [26-28]. In 1970, the first human MPXV infection case was detected in Bokenda, a remote village in the Equatorial province of the DRC, in a nine-month-old baby boy that has not been vaccinated against Smallpox Virus (SPXV) [29-31], and in the same year, six human cases were reported from the DRC, Liberia and Sierra Leone [32]. Since the first decade (between 1970 and 1981), MPXV virus was endemic in the DRC and had spread to other African countries, mainly in Central and West Africa with more than 400 confirmed cases back at the time [32, 33]. More precisely, the first six years were characterized by the spread of these emerging pathogens in six countries with 48 documented cases - 38 cases in the DRC, 4 in Liberia, 3 in Nigeria and only one each in Cameroon, Côte d'Ivoire, and Sierra Leone [34, 35]. Moreover, between 1981 and 1986 this smallpox continued to spread reaching 3838 cases and 33 deaths in Africa [36]. Subsequently, by 1986, these cases were estimated to be more than 400 with mortality rates approaching 10% [35]. After 1986, this infection began to slow down gradually, and between 1993 and 1995, it disappeared completely [34]. Unfortunately, this decline did not last long, as 511 cases were reported in an outbreak in the Lodja and Katako-Kombe health zones of the DRC, between 1996 and 1997 [36].

The first human Monkeypox outbreak outside of Africa was in 2003 in the USA with 47 infected cases, after an infected Gambian rat transmitted the virus to humans [37-39]. Then, from 2005 to 2007, 760 infected individuals were confirmed in the most significant forest coverage zones in the DRC, and another major outbreak of 587 cases occurred between 2014 and 2016 [36]. Recently, this emerging virus drew attention again [40] after confirmation of the first human Monkeypox virus case in a traveler returning from Nigeria by the United Kingdom Health Security Agency (UKHSA) on May 7, 2022, and since that date, it appeared in non-African countries, including Americas, Eastern Mediterranean, European and

Western Pacific regions [4, 41, 42], with more than 17,300 confirmed and suspected cases identified, and over 40,000 infected individuals in 87 countries that were not MPXV endemic, like the United Kingdom (UK), Australia, Belgium, Canada, France, Germany, Italy, the Netherlands, Portugal, Spain, Sweden, and the USA [43, 44]. On the second of June, 2022, 780 MPXV-infected cases were reported in other 27 non-endemic countries [45] and the next day, the WHO announced this virus as an emerging risk of moderate public health concern, but later on June 22, 2022, the World Health Network (WHN) declared the current Monkeypox outbreak a pandemic after the confirmation of 3,417 Monkeypox cases spanning across 58 countries and rapidly spreading across multiple continents [5], and following a series of events, the WHO once again declared this perilous virus a Public Health Emergency of International Concern on July 23 [42, 46]. On October 21 2022, 75,348 confirmed cases were reported in 109 countries worldwide [47], and by December 2022, this number increased to 83,497 laboratory-confirmed cases, 1,694 probable cases, and 72 deaths in 110 countries [48], reaching a total of 85,922 cases as of February 20th 2023 as reported by the Atlanta CDC [49], and 87,113 as of April 24th 2023 as reported by WHO (Figure 1).

Monkeypox virus

Origin and animal's reservoir

MPXV can infect a wide range of animals like birds, reptiles, insects, and mammals, which play the role of intermediate hosts in the natural zoonotic cycle [29, 50-52] but its natural reservoir is still unknown [27, 53]. Till now, this virus has been isolated from wild animals only twice: in 1985 in DRC in a rope squirrel (*Funisciurus anerythrus*), and in sooty mangabey (*Cercocebus atys*) in Ivory Coast in 2012, and hence scientists suggest that these species may be the original reservoir of this emerging virus [36, 53, 54].

Classification and structure

MPXV belongs to the family of *Poxviridae* under the subfamily of *Chordopoxvirinae* in the *Orthopoxvirus* genus, [53, 55-57].

Monkeypox virus has two distinct infectious forms, extracellular enveloped virions (EEVs) and intracellular mature virions (IMVs) (Figure 2) [34, 58, 59]. Electron microscopy of MV shows an ovoid or brick-shaped particle measuring between 200 and 250 nm, surrounded by a 30 nm lipoprotein outer membrane with a tubule or filamentous surface. Also, it has a large double-stranded linear DNA genome with a double concave dumbbell-shaped nucleoprotein. In addition to an envelope, the mature EV has the same constructions as that of MV [36, 37, 60-65].

Genome

MPXV genome is a linear double-stranded DNA measuring about 197 kb with more than 190 non-overlapping open reading frames (ORFs) each of which consists of over 60 amino acid residues [44, 56, 60]. This large genome is bipartite and covalently closed and contains an identical but oppositely oriented 6379 bp inverted terminal repeat (ITR) sequence at the end of the genome [62]. The genes of this virus can be divided into two types, conserving genes which encode all the proteins needed for viral infectious cycle, and the non-conserved genes which are mostly associated with the immune escape of the poxvirus (Figure 3) [34, 65]. Additionally, comparative analysis shows that MPXV has more than 90% nucleotides (around 196.858 base pairs) and 60 amino acid residues similar to other *Orthopoxvirus* [6, 66]. Phylogenetically, the genome of MPXV and Variola virus (VARV) share a high level of sequence similarity (96.6%) and according to this level, it suggests that they did not evolve from one another [55, 67].

Mutations

Monkeypox virus does not present a lot of mutations compared to RNA viruses due to the high stability of their genome and the 3'-5' correction activity of poxvirus exonuclease [55, 67]. Scientists suggest that these mutations may be caused by the Apolipoprotein B mRNA-Editing Catalytic Polypeptide-like 3 (APOBEC3) enzymes, which can cause harmful effects on this virus [35, 55].

Phylogenetically, this Poxvirus is divided into two clades, Clade I (Congo Basin or Central Africa (CA))

Figure 1. Geographical distribution of confirmed and suspected Monkeypox cases until April 24th 2023 reported by the WHO.

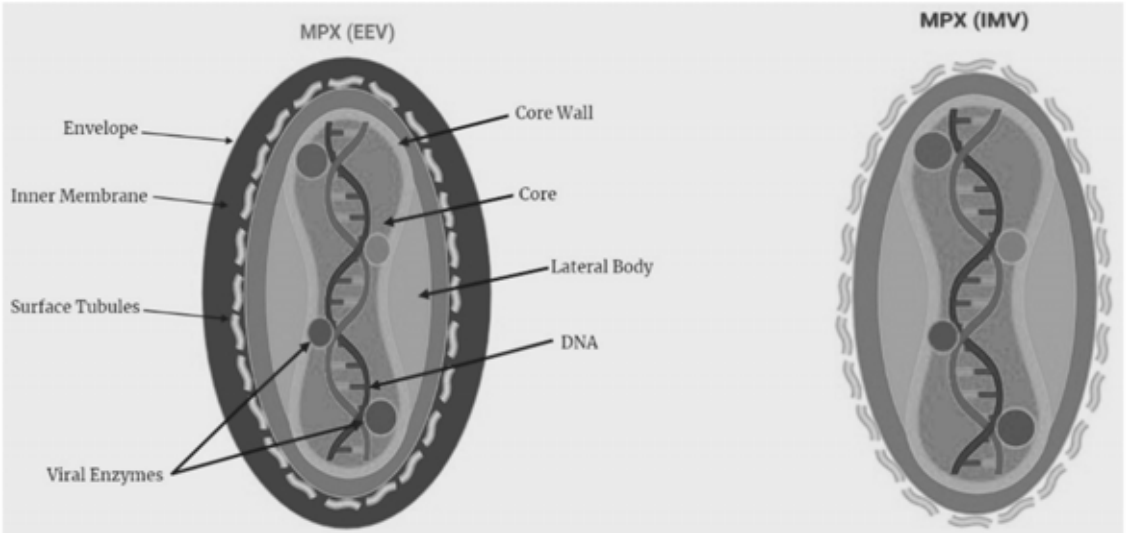

Figure 2. Structure of the two Monkeypox virus forms (EEV and IMV) (Reproduced from Kumar *et al*., 2023, Viruses, 15(4), 937 [80]).

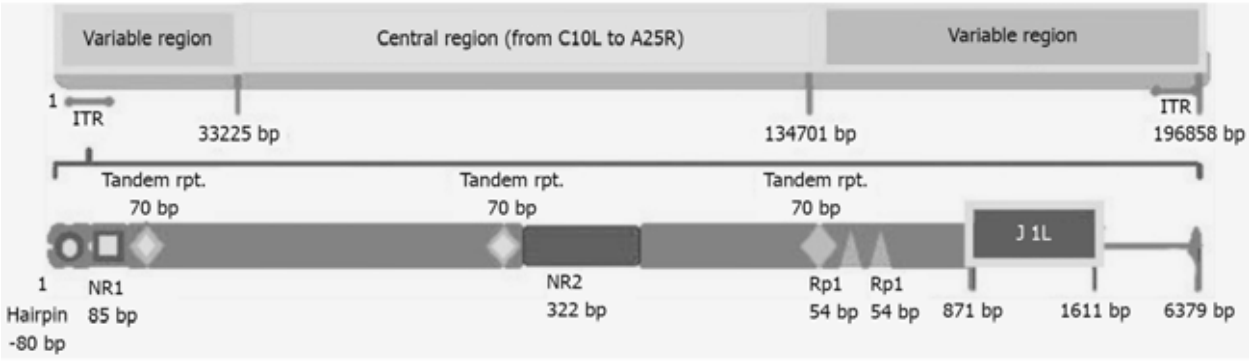

Figure 3. Genome of Monkeypox virus (MPXV) (Reproduced from Beig *et al*., 2022, World Journal of Virology, 11(6), 426-434 [81]).

and Clade II (West Africa (WA)) [44, 54, 68]. A comparative study between the Central African strain (ZAI-96) and three West African strains (SL-V70, COP-58, and WRAIR-61) has revealed a 0.55-0.56% nucleotide difference between the two clades [35, 59, 69]. The CA clade is more virulent than the WA clade [39, 57, 60]. A genomic comparative study between the first WA strain which was isolated in 1971 and another from 2022 MPXV outbreak revealed a nucleotide composition difference of less than 0.06% when compared to another strain [67]. As a result, a novel nomenclature was proposed to classify this virus into three clades, the third one inducing the current outbreak Outside African which has multiples lineages [37]. Another analysis indicated that the 2022 outbreak Monkeypox virus strains contain 46 new consensus mutations, including 24 non synonymous mutations, compared with the Monkeypox virus-2018 strain, and suggested that the lower mortality and higher transmission of these strains are due to these mutations [55].

Life cycle of MPXV

There is no specific tissue tropism of MPXV because it was detected in several tissues [58]. Initially, it infects the lower airway epithelial cells and spreads to lymph nodes, followed by systemic

dissemination through monocytes [67]. Like all Poxviruses, MPXV performs its replication cycle in the cytoplasm of the host cell with the use of a virally encoded RNA polymerase which is uncommon among DNA viruses [52, 55]. This viral cycle is carried through multiple steps, including viral particle entry, genomic replication, assembly, and release (Figure 4) [37].

Viral entry

Scientists suggest that Monkeypox viral entry is associated with host cell type and viral clade, and to date, the specific receptors of this virus are unknown [37], but multiple glycosaminoglycans, such as Heparin Sulfates, Chondroitin, and Laminin, are potential cell surface receptors for the virus, facilitating its attachment to infected cells' surfaces [55, 67, 70]. Next, MPXV enters to the target cell with the use of two different methods; if this particle is found in a neutral medium it will enter by direct fusion, but in low pH, it will use endosomal pathways (micropinocytosis/endocytosis) [35, 37, 67]. Following that, it releases its nucleocapsid (core) into the cytoplasm [71].

Replication

In the cytoplasm, this obligate intracellular virus synthesizes early, intermediate, and late viral mRNA through MPXV-encoded multi-subunit DNA-dependent RNA polymerases (RNAPs) and several host transcription factors and proteins [37, 55, 63]. This stage is followed by the translation of early, intermediate, and late proteins on host ribosome [37, 67].

Assembly and release

This step consists of assembly and differentiation into intracellular mature virions (IMVs) [63], where some of them are released externally by

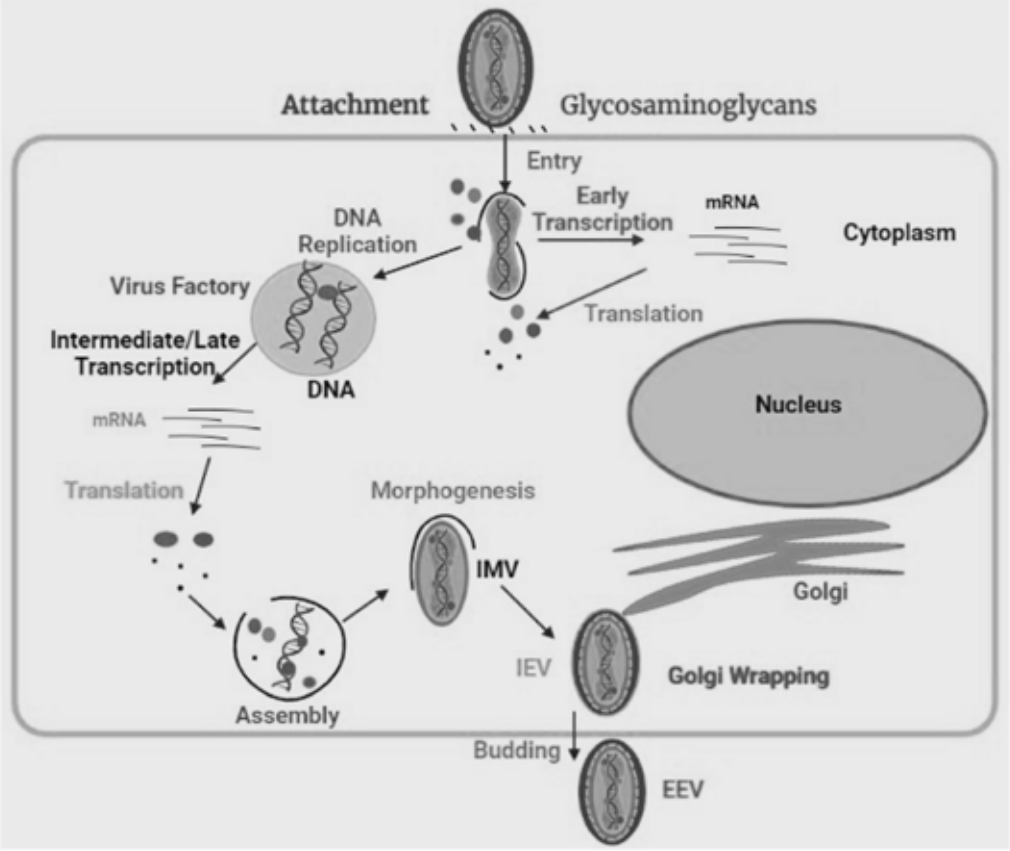

Figure 4. Replication cycle of the MPXV (Reproduced from Kumar *et al*., 2023, Viruses, 15(4), 937 [80]).

cell lysis, and other particles are transported through microtubules toward the endoplasmic reticulum or Golgi to acquire their envelope to form intracellular enveloped viruses (IEVs) which are released from this host by exocytosis [37, 72].

Transmission of MPXV

Monkeypox (MPX) is a highly contagious infectious disease [57] which appears on the WHO list of infectious diseases caused by viruses that have the potential to be endemic or pandemic [73]. Monkeypox virus transmission occurs through two modes, animal-to-human, and human-to-human mode [5, 30]. To date, its exact transmission mode is unknown [27].

Animal-to-human transmission

In the 1980s in DRC, 72.5% of MKPX-infected cases were the result of animal-to-human transmission mode [36]. The individuals who used to sleep outdoors or on the bare ground, particularly those residing in close proximity to a forest, were the primary suspects for this mode of transmission [27, 57, 74]. They could contract this zoonotic virus by coming into direct contact with the blood or bodily fluids of animals carrying the virus, as well as through touching contaminated objects and acquiring coetaneous or mucosal lesions from bites or scratches inflicted by infected animals [39, 58, 74]. Moreover, the consumption of raw meat and using infected animal products like bushmeat promote this type of transmission [34, 52, 75].

Human-to-human transmission

Human-to-human transmission mode was the main cause in most of the cases reported in Nigeria outbreaks (between 2017 and 2018) [36]. wherein the virus transmits between humans through direct contact, muco-cutaneous lesions, body fluids, and continuous exposure to respiratory droplets within a distance of six feet or less for a duration of three hours or more [35, 44, 45]. Additionally, physical contact with contaminated objects or surfaces, and eating or drinking from the same dishes of an infected individual plays a decisive role in Monkeypox spread [27, 74, 75].

This Poxvirus has proven its high ability to transmit through sexual relations, especially intercourse between homosexuals. WHO reported that out of the 55,561 confirmed cases, 89% of them acquired this virus through unsafe sexual activities with men [31, 34, 35]. On the other hand, parents who are infected with MPXV can transmit the virus to their babies through two routes: vertical transmission during pregnancy and close skin contact [62, 74, 75].

The immune system response to monkeypox

Monkeypox virus entry into the target cells triggers a classical immune response against it by the use of both arms of the immune system, innate and adaptive immunity [36].

Innate immunity

To date, the effective roles of innate immune cells like monocytes, macrophages and innate lymphoid cells are unknown [70]. The feature of innate immunity lies in the presence of pattern recognition receptors (PRRs) which are used to initiate an immune response cascade [56, 76], and this represents the first line of defense following active viral infection [59]. Many cells play key roles in this immune response such as natural killer cells which modulate the functions of other immunity cells like T cells through cytokines secretions [36, 58, 59], and dendritic cells (antigen-presenting cells) which migrate to viral replication sites to activate other immune cells [77]. Moreover, this complex system performs a variety of functions, including the removal of cellular debris, the initiation of an inflammatory response, the activation of adaptive immunity, and the recognition of virus-infected cells [63].

Adaptive immunity

After the innate immunity, the virus leads to the activation of adaptive immunity which occurs proximally between 7 to 14 weeks, and 1 year after exposure the immune response progresses from cellular to humoral mechanisms in the initial stages [70, 78]. At the onset of MPX infection, two types of T-cells are engaged: CD4+ helper T lymphocytes (LT4), which recruit CD8+ helper T lymphocytes (LT8) to the sites of viral replication, promoting their differentiation into effector and memory T cells. LT8 cells eliminate infected cells either indirectly by inducing killing cytokines like

Interferon-gamma (IFN-γ) and Tumor Necrosis Factor α (TNF-α), or directly through cell-to-cell contact [77]. Subsequently, the second stage of immune defense takes place under the surveillance of B cells which differentiate into plasma cells that in turn, migrate to immune organs like the lymph nodes, mucus membranes, and bone marrow to produce specific antibodies against MPXV and facilitate their entry to the bloodstream to control the viral spread [77, 79].

Immune evasion

Like other *Orthopoxviruses*, the Monkeypox virus develops many different mechanisms to evade or worsen host immune responses (Figure 5) [58, 60]. This emerging virus improves its ability to prevent apoptosis in infected cells by expressing specific proteins that target the apoptotic pathways [59]. Also, the MPXV genome encodes multiple proteins that promote its immune evasion like B16 which inhibits antiviral type I interferon-induced signaling [67], and A47R which interacts with specific adaptor proteins to inhibit the transcription factors associated with inflammation like the nuclear factor-κB (NF-κB) [60]. In addition, this pathogen can inhibit the activities of natural killer cells by interfering with their activation processes [59]. In addition, the Central African MPXV Zaire strain has the capability to express the Monkeypox Inhibitor of Complement Enzymes (MOPICE), which is encoded by the D14 gene. This protein effectively hinders the activation of the complement cascade [59, 63].

CONCLUSION

The rapid spread of the emerging Monkeypox virus has once again highlighted the need for

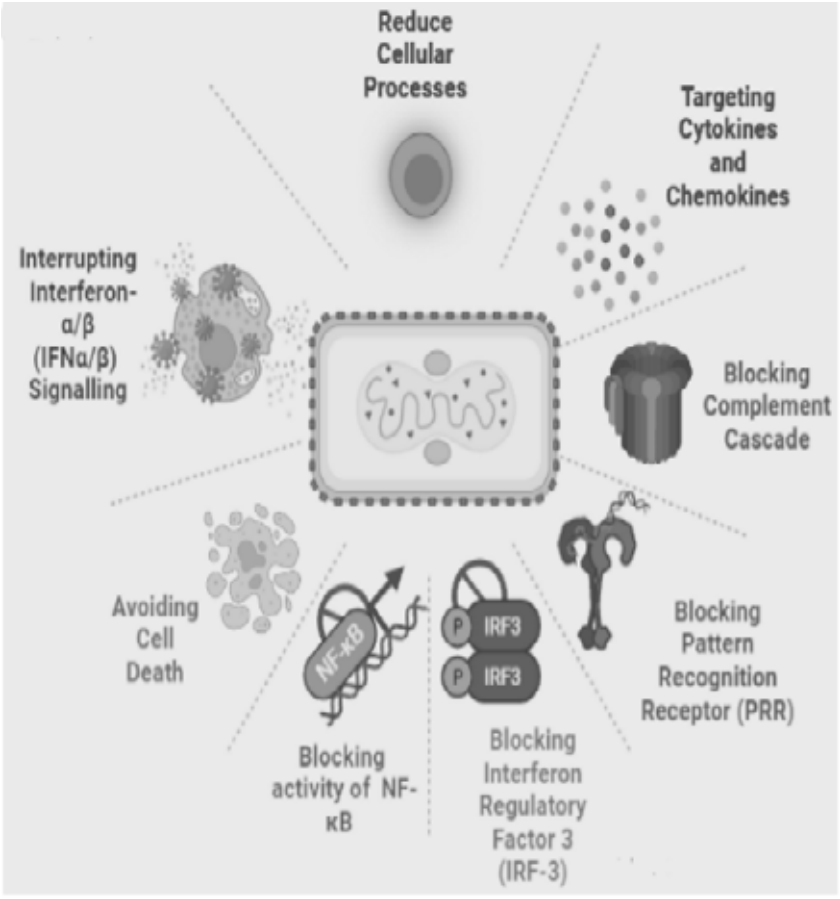

Figure 5. Immune evasion by MPXV (Reproduced from Anwar *et al*., 2023, Life, 13(2), 522 [82]).

rigorous studies to focus on epidemiology, morphology and genetics, as well as the transmission patterns of this virus to understand its infectious cycle and disease. We urge scientists and policymakers to assemble and form proper strategies to contain the recent spread of the virus, and to inform individuals to be more aware, self-conscious, and not to get carried away by fake news and rumors distributed on social media. A pondering question that remains in our minds is: what would be the future of these emerging viruses?

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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AUTHORS' CONTRIBUTIONS

Ilyes Zatla: Conceptualization, manuscript editing, manuscript review, supervision of the project.

Wafa Abid: Literature search, manuscript writing, manuscript editing.

Lamia Boublenza: Manuscript review, supervision of the project.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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